



Virginia Commonwealth University  
VCU Scholars Compass

---

Theses and Dissertations

Graduate School

---

1966

## The Synthesis of 4-Spiro-2-Aryloxazolines of Potential Pharmacological Interest

Paul Waddell Collins

Follow this and additional works at: <https://scholarscompass.vcu.edu/etd>

 Part of the [Chemistry Commons](#)

© The Author

---

Downloaded from

<https://scholarscompass.vcu.edu/etd/4445>

This Thesis is brought to you for free and open access by the Graduate School at VCU Scholars Compass. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of VCU Scholars Compass. For more information, please contact [libcompass@vcu.edu](mailto:libcompass@vcu.edu).

R111  
M489  
COLL  
1966  
C.2  
Vault

THE SYNTHESIS OF 4-SPIRO-2-ARYLOXAZOLINES OF POTENTIAL  
PHARMACOLOGICAL INTEREST

by

Paul Waddell Collins

B. S., University of South Carolina, 1962

Thesis

submitted in partial fulfillment of the requirements for the  
Degree of Doctor of Philosophy in the Department of  
Chemistry and Pharmaceutical Chemistry  
at the Medical College of Virginia  
Richmond, Virginia  
June, 1966

62-00820

This thesis by Paul Waddell Collins is accepted in its present form as satisfying the thesis requirements for the Degree of Doctor of Philosophy.

Date:

Approved:

April 28, 1966

[Redacted]

Advisor, Chairman of Graduate Committee

5/6/66

[Redacted]

5/6/66

[Redacted]

5/6/66

[Redacted]

5/6/66

[Redacted]

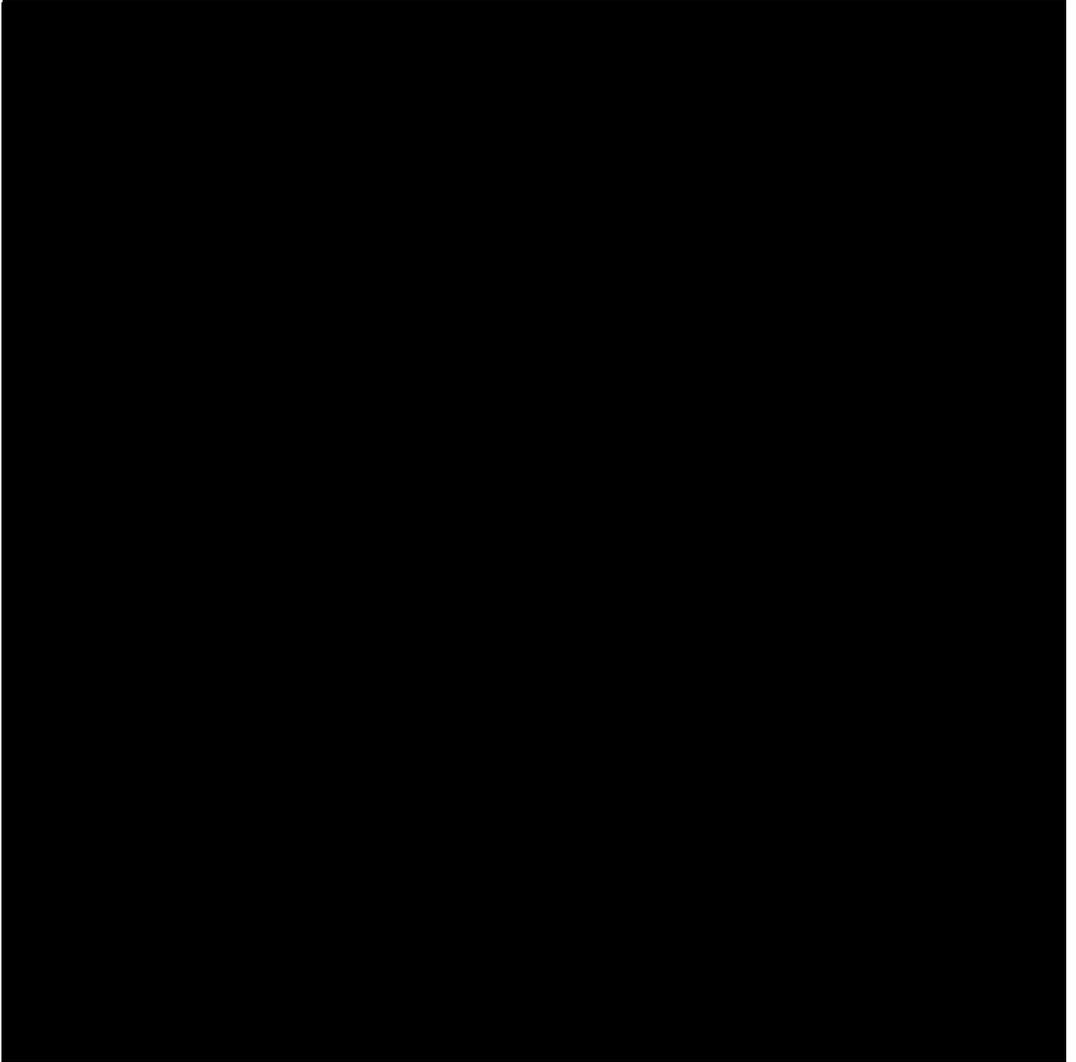
o

Approved:

[Redacted]

Dean of the School of Graduate Studies

CURRICULUM VITAE



## ACKNOWLEDGEMENTS

The author wishes to express his sincere thanks to:

Dr. John Andrako for his patient and prudent supervision of this work, and for his invaluable assistance in the preparation of this thesis;

Dr. J. Doyle Smith for his many timely and helpful suggestions during the course of this research;

Mrs. Annie S. Leeper and Miss Lucy M. Harvie who performed many of the microanalyses required in this research;

The National Institutes of Health for a training grant in medicinal chemistry during the years 1962-1966.

## TABLE OF CONTENTS

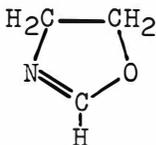
	Page
I. INTRODUCTION.....	1
The Chemistry of 2-Oxazolines.....	1
The Medicinal Activity of 2-Oxazolines.....	9
II. RESEARCH AIM.....	14
III. DISCUSSION.....	20
IV. EXPERIMENTAL.....	43
General.....	43
Preparation of the Cyclopentane Series of 4-Spiro-2-aryl-2-oxazolines.....	44
Common Intermediates.....	44
2-Phenyl-2-oxazoline-4-spirocyclo- pentane.....	47
2-(p-Chlorophenyl)-2-oxazoline-4- spirocyclopentane.....	56
2-(p-Methylphenyl)-2-oxazoline-4- spirocyclopentane.....	62
2-(p-Nitrophenyl)-2-oxazoline-4- spirocyclopentane.....	68
2-(p-Ethoxyphenyl)-2-oxazoline-4- spirocyclopentane.....	73
2-(p-Dimethylaminophenyl)-2-oxazoline- 4-spirocyclopentane.....	79

	Page
Preparation of the 1-Methylpiperidine	
Series of 4-Spiro-2-aryl-2-oxazolines.....	86
Common Intermediates.....	86
1'-Methyl-2-phenyl-2-oxazoline-4- spiro-4'-piperidine.....	92
1'-Methyl-2-(p-methylphenyl)-2- oxazoline-4-spiro-4'-piperidine.....	97
V. SUMMARY.....	99
VI. REFERENCES.....	102

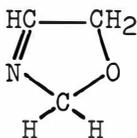
## INTRODUCTION

### The Chemistry of 2-Oxazolines<sup>1</sup>

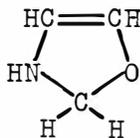
The oxazoline ring system contains one double bond which can occupy three different positions in the ring (I).



2-oxazoline



3-oxazoline



I

4-oxazoline

To distinguish the three isomeric structures, a numerical prefix is employed. The most common system by far is the 2-oxazoline isomer. Indeed, very few 3- and 4-oxazoline compounds are known (1). For this reason 2-oxazolines are often referred to simply as "oxazolines".

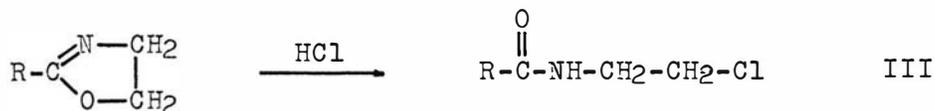
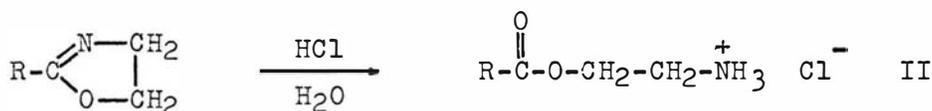
The simpler 2-oxazolines are water miscible liquids. Members of higher molecular weight, however, are frequently low melting solids of low water solubility. The 2-oxazoline ring is, in general, stable to heat. 2-Aryl-2-oxazolines can be successfully distilled at temperatures up to 250° (1). The infrared spectra of 2-oxazoline compounds

---

<sup>1</sup>The chemistry of 2-oxazolines has been reviewed extensively by Cornforth (1) and by Wiley and Bennett (3).

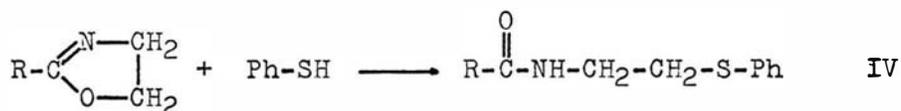
display a band between 5.92 and 6.10 microns (1690 - 1640  $\text{cm}^{-1}$ ) which is characteristic of the imine group ( $\text{C}=\text{N}$ ) of the ring (2).

The 2-oxazolines are ring analogs of imino esters ( $\text{R}-\text{C}=\overset{\text{NH}}{\text{OR}}$ ). They behave chemically, therefore, in a manner quite similar to the imino esters. 2-Oxazolines are weak bases and are soluble in dilute acid. Picrates of the 2-oxazolines can be prepared and are often used for purposes of characterization. A few cases of quaternary salt formation have been reported (3). The salts of 2-oxazolines are readily hydrolyzed in hot dilute acid or in boiling water to  $\beta$ -acyloxyamine salts (II). With concentrated acid 2-oxazolines may undergo a different cleavage reaction (III). For example, 2-phenyl-2-oxazoline

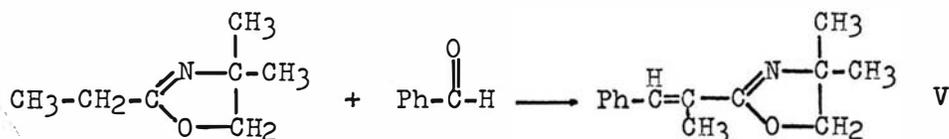


on evaporation to dryness with concentrated hydrochloric acid gives  $\beta$ -chloroethylbenzamide (4). It is known that the ring is hydrolyzed by attack of a water molecule at position "2", while attack of a chloride ion at position "5" initiates the transformation to the  $\beta$ -chloroethylamide (5). With water and chloride ion present in the reaction medium, both reactions are possible and a

competition between the two, results. A predominance of water, as in dilute acid, would thus favor II, while a predominance of chloride ion, as in concentrated hydrochloric acid, would favor III. Ring cleavage according to III may be accomplished also by refluxing a solution of a 2-oxazoline compound in an organic solvent which has been previously saturated with hydrogen chloride gas. Other nucleophilic groups will attack the ring in a fashion analogous to the chloride ion. Wehrmeister (6), for example, obtained a  $\beta$ -(phenylmercapto)-alkylamide on treatment of a 2-alkyl-2-oxazoline with thiophenol(IV).



2-Oxazolines are not cleaved readily in aqueous alkali; 65% of a sample of 2-phenyl-2-oxazoline was recovered after three hours of boiling in 10% sodium hydroxide (7). The  $\alpha$ -hydrogen atoms of an alkyl group attached to the 2-oxazoline ring at the "2" position are acidic. Wehrmeister (8) demonstrated this acidity by condensing benzaldehyde with 4,4-dimethyl-2-ethyl-2-oxazoline (V).



Based on the limited evidence available, it has been concluded that the 2-oxazoline ring is fairly stable to oxidizing agents (3). 2-Phenyl-2-oxazoline has been successfully converted to 2-(m-nitrophenyl)-2-oxazoline in a nitric acid-sulfuric acid mixture (9). Billman and Parker (10) used potassium permanganate to oxidize 4-methyl-4-hydroxymethyl-2-phenyl-2-oxazoline to the corresponding acid without ring cleavage.

The most commonly employed syntheses of 2-oxazolines involve the removal of either water from ( $\beta$ -hydroxyalkylamides (VI) or halogen acid from ( $\beta$ -haloalkylamides (VII) with resultant ring closure.

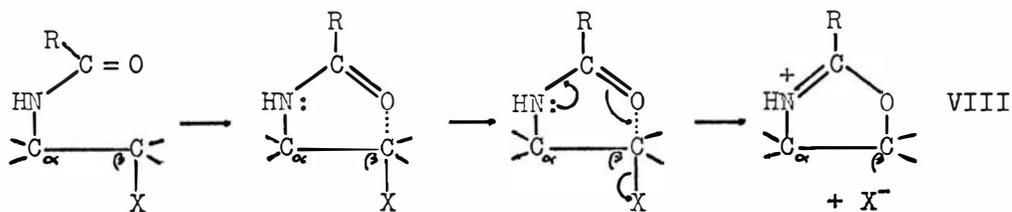


Dehydration of ( $\beta$ -hydroxyalkylamides (VI) can be accomplished by azeotropic removal of water from a refluxing solution of the hydroxyamide in benzene or toluene (11). The more common procedure, however, involves the use of a dehydrating agent such as thionyl chloride, sulfuric acid, or phosphorus pentoxide. Of these, thionyl chloride is the preferred agent. With it, 2-oxazoline compounds can be prepared at room temperature, in high

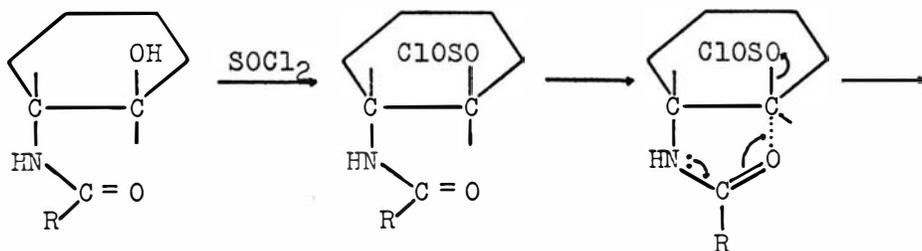
yields, and with a minimum of work up effort. In addition to these agents, *p*-toluenesulfonyl chloride, in the presence of pyridine, has been shown to effect ring closure at room temperature and in good yield (12).

Dehydrohalogenation of  $\beta$ -haloalkylamides (VII) is usually carried out by heating the haloamides with sodium hydroxide in aqueous ethanol. However, both pure aqueous and pure alcoholic media have been employed with a variety of bases (1). Since  $\beta$ -haloalkylamides are usually prepared from the corresponding  $\beta$ -hydroxyamides, this method is an indirect one in many cases. It finds utility in the synthesis of 2-oxazolines which can not be readily prepared from the corresponding  $\beta$ -hydroxyamides. In addition, the products from this method can serve as evidence for the correctness of the assignment of the 2-oxazoline structure to products isolated from the more direct dehydration methods.

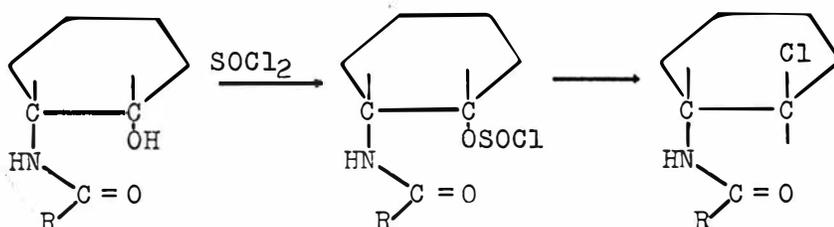
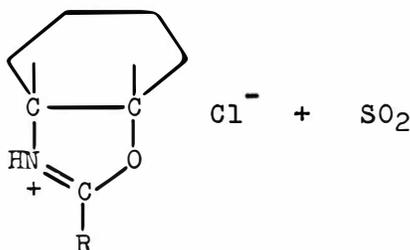
Dehydrohalogenation of  $\beta$ -haloamides and dehydration of  $\beta$ -hydroxyamides with thionyl chloride, *p*-toluenesulfonyl chloride and most probably sulfuric acid occur by the inversion cyclization mechanism (13). This mechanism involves the backside nucleophilic attack of the amide carbonyl oxygen at the  $\beta$ -carbon atom with concomitant displacement of an anion X ( $-\text{Cl}$ ,  $-\text{OSOCl}$ , or  $-\text{O}_3\text{S-Ph-CH}_3\text{-p}$ ) from the  $\beta$ -carbon atom (VIII). Stereochemical studies on 2-aminocyclohexanol derivatives have provided substantial evidence for the correctness of this mechanism. The trans



isomer of 2-benzamidocyclohexanol gives, on treatment with thionyl chloride, the cis-2-oxazoline (IX a). The cis-2-benzamidocyclohexanol, on the other hand, gives no oxazoline because of its inability to assume the conformation necessary for reaction to occur (14) (IX b).

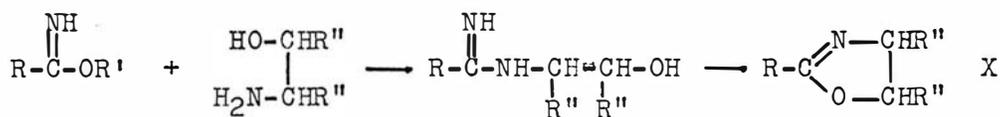


IX a

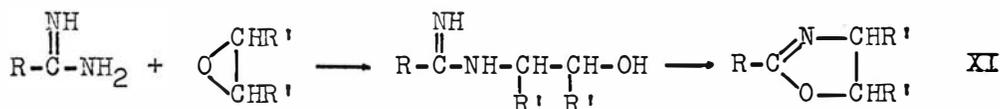


IX b

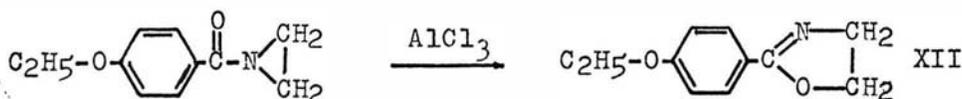
There are numerous miscellaneous methods by which 2-oxazolines have been prepared. Gabriel and Neumann (15) synthesized a 2-oxazoline by treatment of the iminoester of a  $\beta$ -chloroalcohol with sodium hydroxide. Bockemühl and Knoll (16) condensed an iminoester with a  $\beta$ -hydroxyamine to obtain a 2-oxazoline (X). It has been established that this reaction proceeds through an intermediate N-(2-hydroxyalkyl)-amidine (17). Lambert and Kristofferson (18)



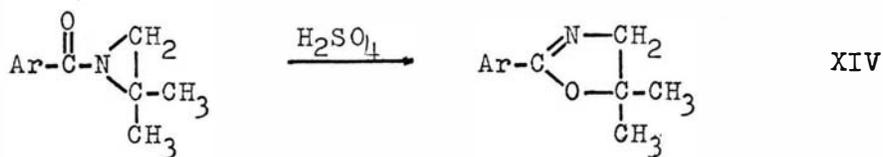
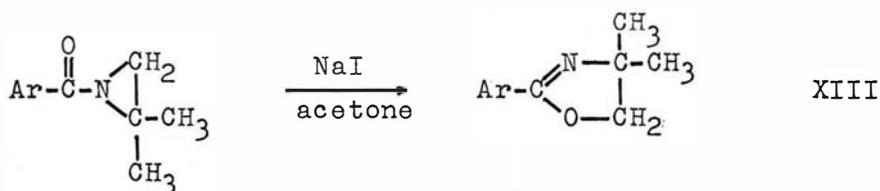
treated an amidine with an epoxide to obtain a N-(2-hydroxyalkyl)-amidine which was then converted without isolation to the 2-oxazoline by heating the reaction mixture (XI).



Heine and Proctor (19) have reported the synthesis of 2-(p-ethoxyphenyl)-2-oxazoline by isomerization of p-ethoxybenzoylethylenimine with aluminum chloride in heptane (XII). Heine et al. (20) described the isomeri-



zation of 1-aryl-2,2-dimethylaziridines to 2-aryl-4,4-dimethyl-2-oxazolines with sodium iodide in acetone (XIII) and to 2-aryl-5,5-dimethyl-2-oxazolines with sulfuric acid (XIV). High yields were obtained in both cases.



The Medicinal Activity of 2-Oxazolines

The widespread occurrence of the atomic sequence XV in natural as well as synthetic drugs is well known. Such



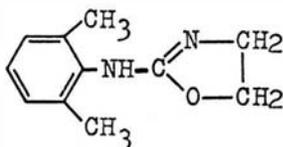
biologically active compounds as acetylcholine, epinephrine, many of their respective analogues, local anesthetics, and antihistamines contain this sequence of atoms in their structures. Additionally, the presence of a trigonal carbon atom as part of a carbonyl or imine function is desirable or necessary for activity in many drugs. The 2-oxazoline ring (XVI) contains both the atomic sequence XV and a trigonal carbon atom. The pres-



ence of both these functions may well be responsible for the numerous and diverse physiological actions which the derivatives of 2-oxazoline possess.

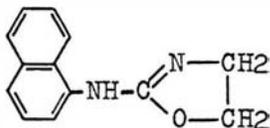
The first medicinally active 2-oxazoline derivatives to be reported were synthesized by Engelmann (21) in 1936. He prepared a series of 2-(p-alkoxyphenyl)-2-oxazolines which possessed appreciable local anesthetic activity. The following year Leffler and Adams (9) prepared a series of

substituted 2-(aminophenyl)-2-oxazolines which also exhibited local anesthetic properties. The best of these was 2-(m-aminophenyl)-2-oxazoline which was equally as effective as procaine and approximately one third as toxic. More recently, Guidicelli et al. (22) have reported that 2-(2,6-dimethylphenylamino)-2-oxazoline (XVII) is somewhat stronger than cocaine as a local anesthetic.



XVII

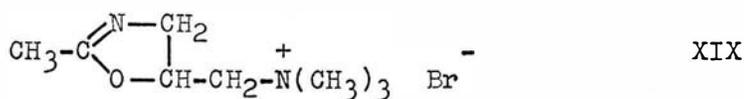
2-Oxazolines have been shown also to possess anticholinesterase activity (23). 2-Amino-2-oxazoline and 2-(1-naphthylamino)-2-oxazoline (XVIII) are powerful inhibitors of acetylcholinesterase. Even 2-methyl-2-oxazoline displayed measurable activity.



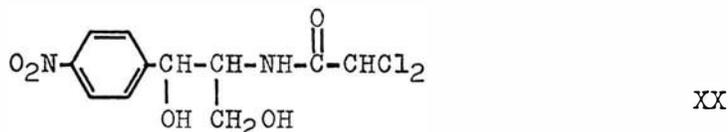
XVIII

Belleau et al. (24) in their studies on the cholinergic receptor, discovered that 5-trimethylammoniummethyl-2-methyl-2-oxazoline bromide (XIX) possessed potent muscarinic properties. On guinea pig ileum, this compound

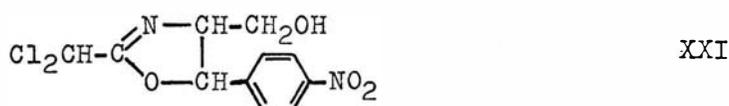
elicited a response equal to that of acetylcholine.



2-Oxazoline derivatives of chloramphenicol (XX)



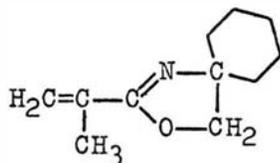
have been utilized both in the synthesis and the configurational analysis of this antibiotic (25). There are reports that 2-oxazoline derivatives of chloramphenicol possess medicinal activity themselves. Rocky Mountain spotted fever, a rickettsial disease, was clinically suppressed by (+)-threo-(2-dichloromethyl)-5-(p-nitrophenyl)-4-hydroxymethyl-2-oxazoline (26) (XXI) which has the same configuration as the active stereoisomer of chloramphenicol. The (-)-threo-isomer of XXI was reported to



be 25% as effective as chloramphenicol against a selected group of bacteria (27). Doubts that the oxazoline structure is the active entity in these and similar experiments have been expressed on the basis that the oxazoline ring of these compounds readily undergoes hydrolysis which results

in the formation of chloramphenicol (25).

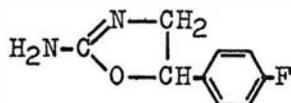
De Benneville and Luskin (28) have reported that 4,4-dimethyl-2-vinyl-2-oxazoline, 4,4-dimethyl-2-isopropenyl-2-oxazoline, and 2-isopropenyl-2-oxazoline-4-spiro-cyclohexane (XXII) are effective fungicides.



XXII

The antithyroid potency in man of 2-mercapto-2-oxazoline is 75% of that of thiouracil (29). The oxazoline compound, however, is slightly less than one tenth as active as 1-methyl-2-mercaptoimidazole (methimazole) which is currently a widely used antithyroid drug.

Of considerable interest in recent years have been the derivatives of 2-amino-2-oxazolines. Poos et al. (30) synthesized a series of 2-amino-5-aryl-2-oxazolines which exhibit typical sympathomimetic actions in the rat and dog (31). In particular, these compounds are potent anorexic agents. One derivative, 2-amino-5-(p-fluorophenyl)-2-oxazoline (XXIII), is four times as potent as (+)-amphetamine in appetite suppressant activity. These compounds are believed to act indirectly by release of endogenous catecholamines (31).



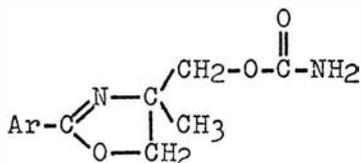
XXIII

N-substituted-2-amino-2-oxazolines such as 2-phenyl-amino-2-oxazoline and 2-(1-naphthylamino)-2-oxazoline (XVIII) have been reported to have vasoconstrictor properties (32). The latter compound is claimed to be two to three times as potent as naphthazoline (2-(1-naphthylmethyl)-imidazoline) and less toxic.

In contrast to the description of 2-amino-2-oxazolines thus far is the report by Bloom (33) that 2-(1-naphthylamino)-2-oxazoline (XVIII) is a powerful central nervous system depressant. This compound exerted a strong sedative action in white mice at a dose of 0.1 mg./Kg. (34). Later patents by Bloom (35) describe numerous N-substituted-2-amino-2-oxazolines which were found to be tranquilizers and potentiators for anesthetics, analgesics and hypnotics.

Moffett (36) prepared a single oxazoline compound, 2-(3,4,5-trimethoxyphenyl)-2-oxazoline, in a large series of polymethoxyphenyl esters and amides. This oxazoline compound exhibited central nervous system depression in mice at a dose of 100 mg./Kg.

Rosnati and Misiti (37) prepared a series of 2-aryl-4-methyl-4-(carbamoyloxymethyl)-2-oxazolines (XXIV) which they report to have muscle relaxant and sedative properties combined with low toxicity.



XXIV

## RESEARCH AIM

Antitussive properties are possessed by a variety of drugs. In addition to morphine and its derivatives, certain sympathomimetics, antispasmodics, antihistamines, tranquilizers, ganglionic blocking agents and local anesthetics exhibit antitussive activity (38).

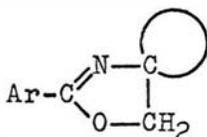
The molecular modification of some members of all these pharmacological classes has led to a tremendous number of synthetic, non-narcotic antitussive agents with wide variation in structure. However, only a few of these compounds are more potent than codeine and most, are weaker. Moreover, many of these synthetic agents retain the undesirable side effects of the prototypes from which they were derived.

The term "antitussive" has been defined (39) as a drug which acts to raise the threshold of the cough center in the brain, or which acts peripherally in the respiratory tract to reduce the number of impulses which pass to the cough center. It is quite possible, however, that more than a single site of action exists both centrally and peripherally. The existence of several receptor sites, each with its own structural requirements for an active pharmacophoric moiety, is certainly supported by the wide variety of structures which have antitussive activity. The combination of multiple receptor sites and the diversity

of structures among active compounds prevent an accurate assessment of what structural features are necessary and/or sufficient to elicit an antitussive response. Indeed, until more fundamental studies have been carried out on the physiological and pathological aspects of the cough reflex and until more specific and accurate methods of pharmacological testing of compounds for antitussive activity are developed, well-defined structure-activity relationships for each site of action can not be established (38).

At present, therefore, the design of potential antitussive compounds is not particularly limited by theoretical considerations or structure-activity requirements.

No reports of the synthesis or biological screening of 4-spiro-2-aryl-2-oxazolines (XXV) were found in a thorough search of the literature.

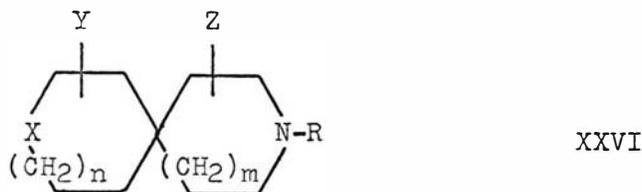


XXV

Spiro compounds or spirans consist of a bicyclic system in which the two rings have one atom in common. The respective planes of two rings fused in such a manner lie at right angles to one another, and thus spiro compounds have an unusual molecular shape.

A number of medicinal compounds contain a spiro function as part of their structures. Most of these are simple modifications of compounds of known activity. Examples

are spirobarbiturates (40), spirohydantoins (41) and spirohydrothiazides (42). In recent years, however, a variety of potent pharmacological properties have been discovered in a large group of aza- and diazaspirans (43) (44) of general formula XXVI. Structural variations of XXVI include derivatives in which:  $n = 0, 1, \text{ or } 2$ ;  $m = 0 \text{ or } 1$ ; Y and Z = hydrogen or alkyl; X = carbon, oxygen, nitrogen or sulfur; R = alkyl, acyl, aralkyl, alkynyl, or amino. Certain of these compounds are active as tranquilizers,

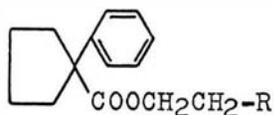


hypotensives, antineoplastic agents, anti-inflammatory agents and local anesthetics.

In view of the diversity of physiological activities generally observed in spiro compounds and in 2-aryl-2-oxazolines, it seemed reasonable that 4-spiro-2-aryl-2-oxazolines should possess interesting pharmacological properties.

Two of the most prevalent monocyclic ring systems found in antitussive drugs are the cyclopentane and N-alkylpiperidine systems. Several synthetic non-narcotic antitussives contain the cyclopentane ring. Two of the earliest discovered agents, caramiphen (XXVII a) and carbetapentane (XXVII b) are both derivatives of

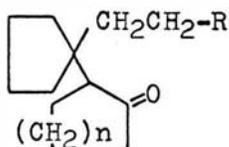
1-phenylcyclopentane-1-carboxylic acid. Antitussive



XXVII

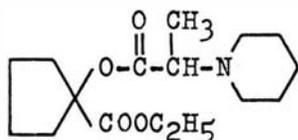
a.  $R = N(C_2H_5)_2$       b.  $R = OCH_2CH_2N(C_2H_5)_2$

activity has been reported (45) for a series of compounds of general formula XXVIII. Derivatives in which n was zero or one and R was diethylamino, piperidino, or morpholino were among the most potent members. Ellis et al. (46)



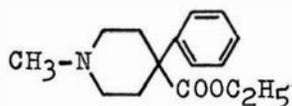
XXVIII

prepared and tested for antitussive activity a large number of derivatives of 1-hydroxycyclopentane-1-carboxylic acid and 1-aminocyclopentane-1-carboxylic acid. The most potent and least toxic of these compounds was ethyl 1-(2-piperidinopropionoxy)cyclopentane-1-carboxylate (XXIX) which was half as strong as codeine.



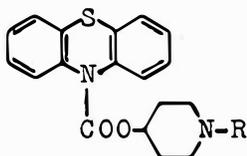
XXIX

The N-alkylpiperidine ring is found in numerous synthetic narcotic compounds which possess antitussive properties. Meperidine (XXX) is a classic example.

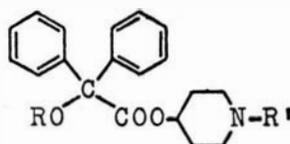


XXX

N-alkyl-4-hydroxypiperidine esters of both phenothiazine-10-carboxylic acid and alkoxydiphenylacetic acids (XXXI) also exhibit antitussive activity (47). Compounds of the



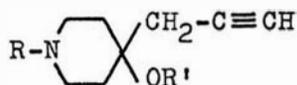
R = alkyl



XXXI

R = R' = alkyl

general structure XXXII in which R is alkyl, aralkyl, phenoxyalkyl, or alkoxyalkyl and R' is acyl or carbamoyl are reported to have potent antitussive properties (48).

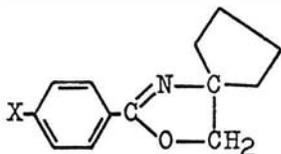


XXXII

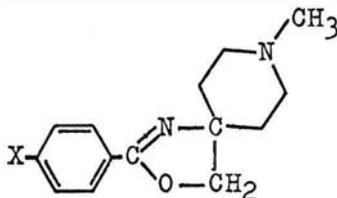
On the basis of this evidence, it was felt that the combination in a spiro bicyclic structure of the 2-oxazoline system with the cyclopentane and N-methylpiperidine systems

respectively, might afford compounds having antitussive activity.

Thus the aim of this research was the synthesis of two series of 4-spiro-2-aryl-2-oxazolines (XXXIII) in which X is: -H, -Cl, -CH<sub>3</sub>, -NO<sub>2</sub>, -OC<sub>2</sub>H<sub>5</sub>, or -N(CH<sub>3</sub>)<sub>2</sub>.



XXXIII

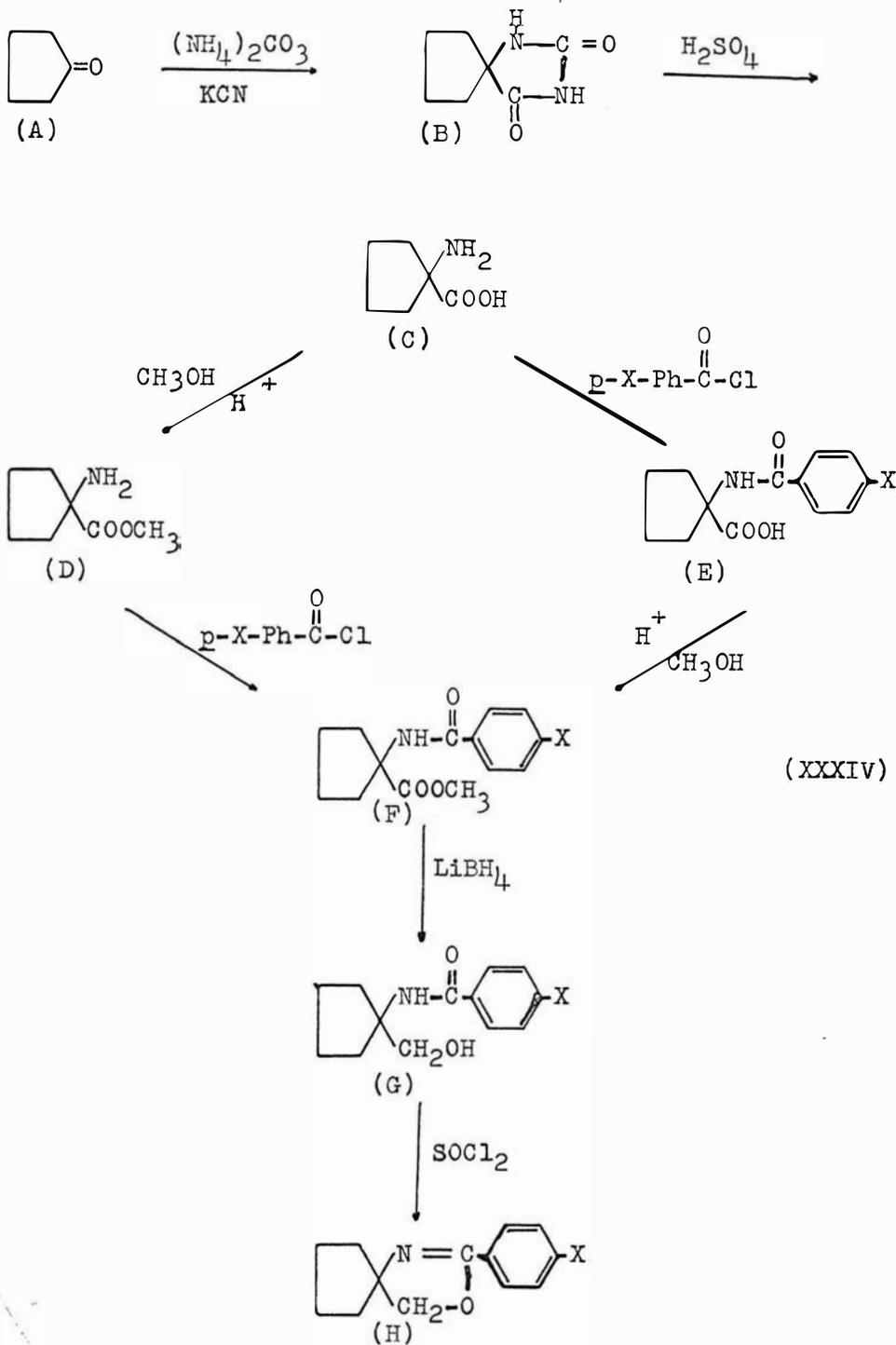


## DISCUSSION

The synthesis of the series of 2-aryl-2-oxazoline-4-spirocyclopentanes was accomplished by the sequence of reactions outlined in XXXIV (page 21). The p-phenyl substituents used in this series were selected on the basis of their electron-donating or -withdrawing abilities in order to have all degrees of electronic influence represented. In many cases the use of substituents selected on this basis permits the determination of the direction and degree of influence which electron distribution may have on the biological activity of a particular structure.

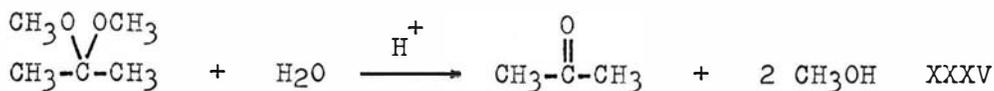
The dimethylamino group was chosen also for another reason. The presence of an additional functional group in a molecule often leads to preparative difficulties not encountered in the parent compound. It was felt that the experience gained in preparing this derivative would be of value in the synthesis of the 1-methylpiperidine series of spirooxazolines since both contain a tertiary amino group.

In XXXIV the hydantoin (B), the amino acid (C), and the amino ester (D) are known compounds and were prepared according to known procedures. To minimize the possibility of cleavage of the amide bond, the amido acids (E) were esterified at room temperature by treatment with a mixture of 2,2-dimethoxypropane (acetone dimethyl ketal), methanol and concentrated hydrochloric acid. The ketal functions



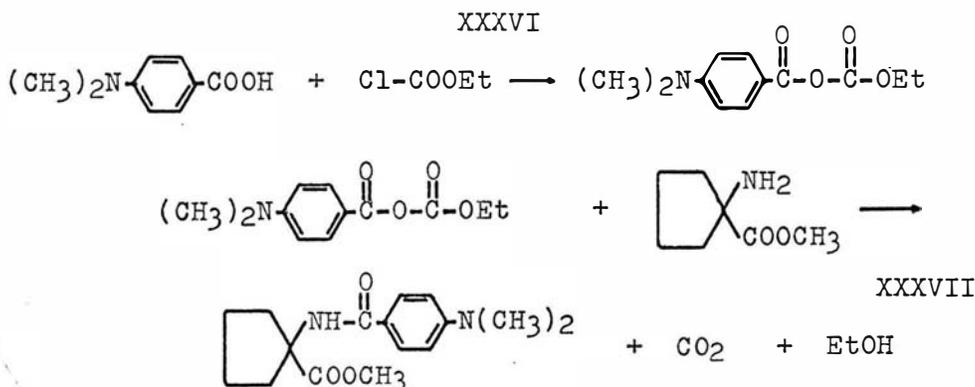
X = -H, -Cl, -CH<sub>3</sub>, -NO<sub>2</sub>, -OC<sub>2</sub>H<sub>5</sub>, -N(CH<sub>3</sub>)<sub>2</sub>

as a water scavenger; its reaction with water is illustrated in XXXV.



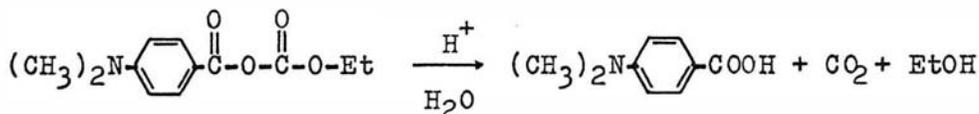
The amido ester (F) was prepared from both the amino ester (D) and the amido acid (E) only in the case of the phenyl and p-ethoxyphenyl derivatives. With both derivatives the identity of the products from the respective starting materials was established by determination of mixture melting points and comparison of their infrared spectra. With the exception of the p-dimethylamino derivative, the remainder of the amido esters (F) were prepared exclusively from the respective amido acids (E).

The synthesis of the p-dimethylaminobenzamido ester (F) was first attempted by preparation of a mixed carbonic anhydride of p-dimethylaminobenzoic acid (XXXVI) and subsequent treatment of this product with 1-amino-1-carbomethoxycyclopentane (D) (XXXVII). The several attempts to



prepare the amido ester (F) by this procedure failed. In each case, however, there was isolated a solid compound which was shown to be a *p*-dimethylaminobenzoic-carbonic anhydride. The structural assignment for this compound was based on its physical properties, infrared spectrum and elemental analysis. The infrared spectrum was particularly valuable in the establishment of the structure of this compound. The spectrum possessed carbonyl peaks at 5.55 and 5.77 microns (1802 and 1733  $\text{cm}^{-1}$ ) the presence and separation of which are characteristic of an anhydride structure (49). Any contribution of the cyclopentane compound to the structure of the anhydride was eliminated from consideration by the isolation of the anhydride from the reaction mixture before the cyclopentane amino ester was added. Upon addition of a few drops of concentrated hydrochloric acid to a pure sample of the anhydride compound on a watch glass there occurred an immediate and vigorous evolution of gas. From the residue *p*-dimethylaminobenzoic acid was isolated. Although no special effort was made to identify the gas, it is reasonable to assume that it was carbon dioxide. The reaction is given in XXXVIII.

## XXXVIII

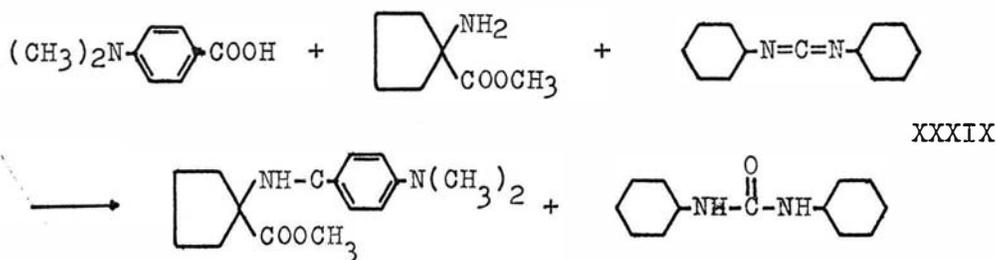


It should be noted that in a successful synthesis involving a mixed anhydride the addition of the amine to

the anhydride is followed by evolution of carbon dioxide. No evolution of gas was observed in any of the attempts made in the present work. The situation appears to be, then, a case of the successful formation of the mixed carbonic anhydride and the subsequent failure of the anhydride to react with the cyclopentane amino ester.

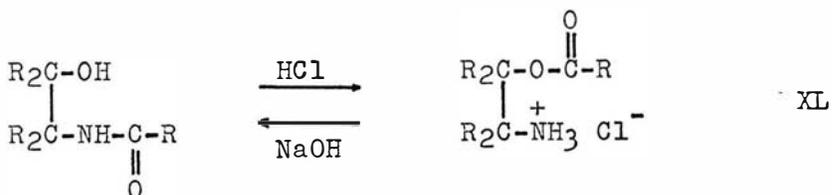
Although mixed carbonic anhydrides were originally thought to be too unstable to exist at room temperature, some of these compounds, particularly substituted benzoic acid derivatives, have been demonstrated to be quite stable (49). Moreover, electron-donating groups on the phenyl ring of these anhydrides stabilize them to nucleophilic attack. Thus the failure of the p-dimethylaminobenzoic carbonic anhydride to react with the cyclopentane amino ester can be explained, at least partially, on the basis of the stability induced in the structure by the electron-donating dimethylamino group.

1-(p-Dimethylaminobenzamido)-1-carbomethoxycyclopentane was successfully prepared by the use of dicyclohexylcarbodiimide to couple p-dimethylaminobenzoic acid with 1-amino-1-carbomethoxycyclopentane. The reaction is illustrated in XXXIX.

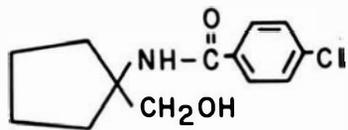
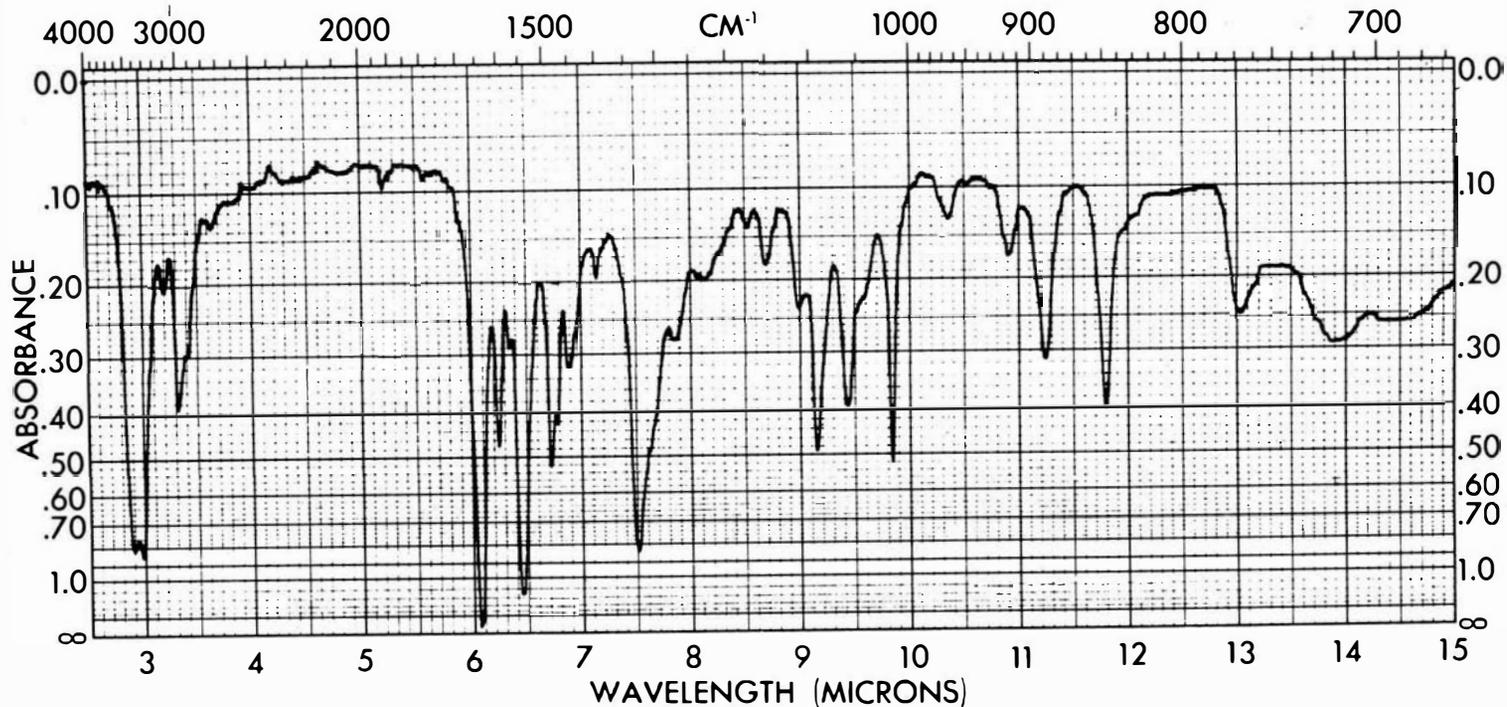


Lithium borohydride, an agent which will selectively reduce an ester function in the presence of an amide bond, was employed to reduce all the amido esters (F) to the corresponding amido alcohols (G). Because solid lithium borohydride is difficult to store and is readily decomposed by moisture, it was produced in situ from potassium borohydride and lithium chloride. The success of the reductions in each case was ascertained by examination of the infrared spectra. All the spectra were essentially void of absorption in the ester carbonyl region, but each possessed a peak corresponding to the alcoholic OH group. A typical spectrum is reproduced on page 26.

$\beta$ -Acylaminoalkanols are known to undergo nitrogen to oxygen acyl migration in an acid medium to give the corresponding  $\beta$ -acyloxyalkylamine salts. Moreover,  $\beta$ -acyloxyalkylamine salts when placed in an alkaline medium rearrange by oxygen to nitrogen acyl migration to  $\beta$ -acylaminoalkanols. These reactions are illustrated in XL.

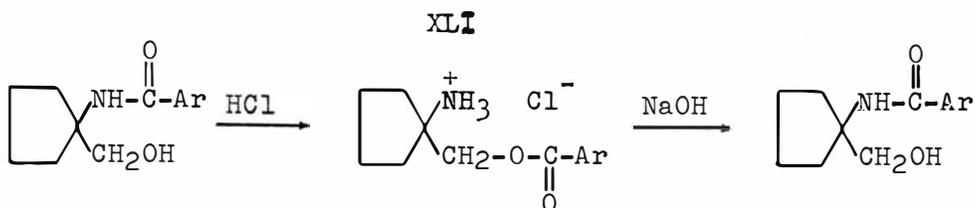


The assignment of an amido alcohol structure to a compound can be verified by the demonstration of that compound's ability to undergo nitrogen to oxygen acyl migration and



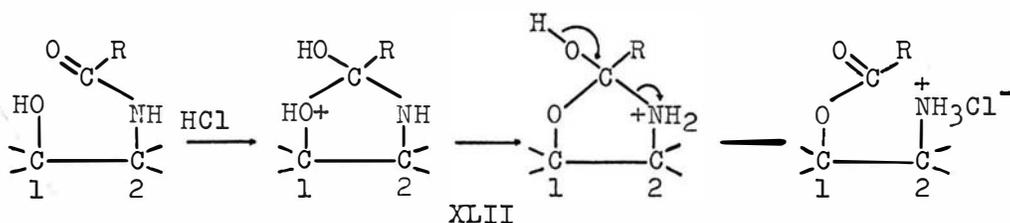
by the subsequent conversion of the migration product to the original compound by oxygen to nitrogen acyl migration.

Such a test of structure was performed on each of the amido alcohols (G) in this series. The conversions are illustrated in XLI. The structure of each 1-amino-1-

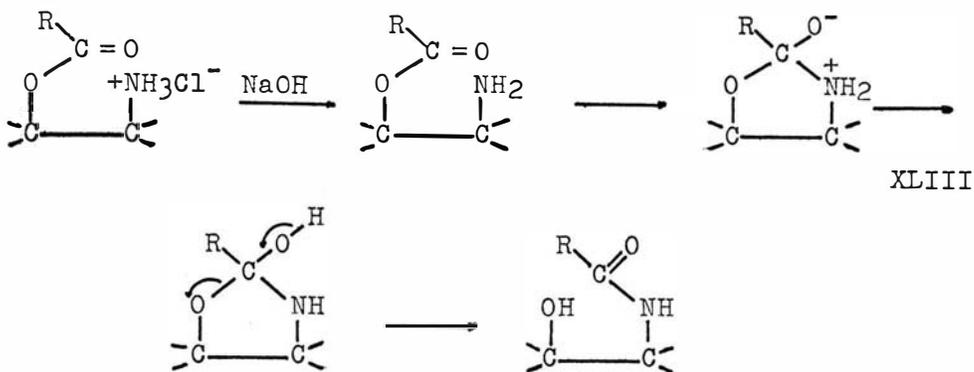


cyclopentylmethyl p-substituted benzoate hydrochloride was established by examination of its infrared spectrum and by its elemental analysis. A sample of each hydrochloride was treated with dilute sodium hydroxide to afford a compound whose identity with the original amido alcohol (G) was established by determination of the melting point of a mixture of the two compounds and by comparison of their infrared spectra.

The mechanisms of these two rearrangements have been the object of numerous researches. Stereochemical studies (50) have established the mechanism which is operative in most nitrogen to oxygen acyl migration reactions. This mechanism, which is outlined in XLII, involves retention



of configuration at carbons 1 and 2. The mechanism for oxygen to nitrogen acyl migration (51), which is the reverse of that for nitrogen to oxygen acyl migration, is illustrated in XLIII.

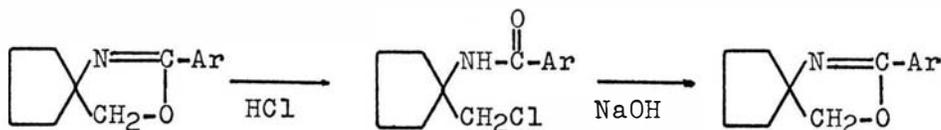


All the oxazolines (H) were obtained in good yield and in relatively pure form by treatment of the corresponding amido alcohols (G) with thionyl chloride. The mechanism of this reaction is discussed on page 5. The preparation of the unsubstituted oxazoline (X = -H) was attempted originally by treatment of the amido alcohol (G) with *p*-toluenesulfonyl chloride in pyridine. Every attempt produced only a small amount of the oxazoline, however, and this method was not tried with the other derivatives. The small quantity of 2-phenyl-2-oxazoline-4-spirocyclopentane hydrochloride isolated from this reaction was shown to be identical with that obtained from the thionyl chloride reaction by determination of the melting point of a mixture of the two products and by comparison of their infrared spectra.

It was mentioned previously (page 2) that 2-oxazolines

may be cleaved to the corresponding  $\beta$ -chloroamides by heating them in an organic solvent which has been previously saturated with hydrogen chloride gas. It was also mentioned that 2-oxazolines may be prepared by heating  $\beta$ -chloroamides in an alkaline medium (page 5). These reactions are illustrated in XLIV. It should be noted that

## XLIV



the mechanism for the cleavage of the oxazoline ring with hydrogen chloride is the reverse of the mechanism which is operative in the formation of the oxazoline ring from either an amido alcohol with thionyl chloride or a  $\beta$ -chloroamide with alkali.

The interconvertibility of the 2-oxazolines and  $\beta$ -chloroamides was utilized to verify the 2-oxazoline structure of the products obtained from the thionyl chloride reactions just as the relationship between the amido alcohols and the  $\beta$ -acyloxyalkylamine hydrochlorides was used to obtain further proof for the structure of the amido alcohols.

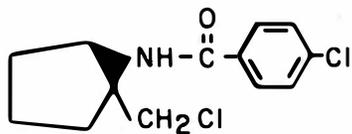
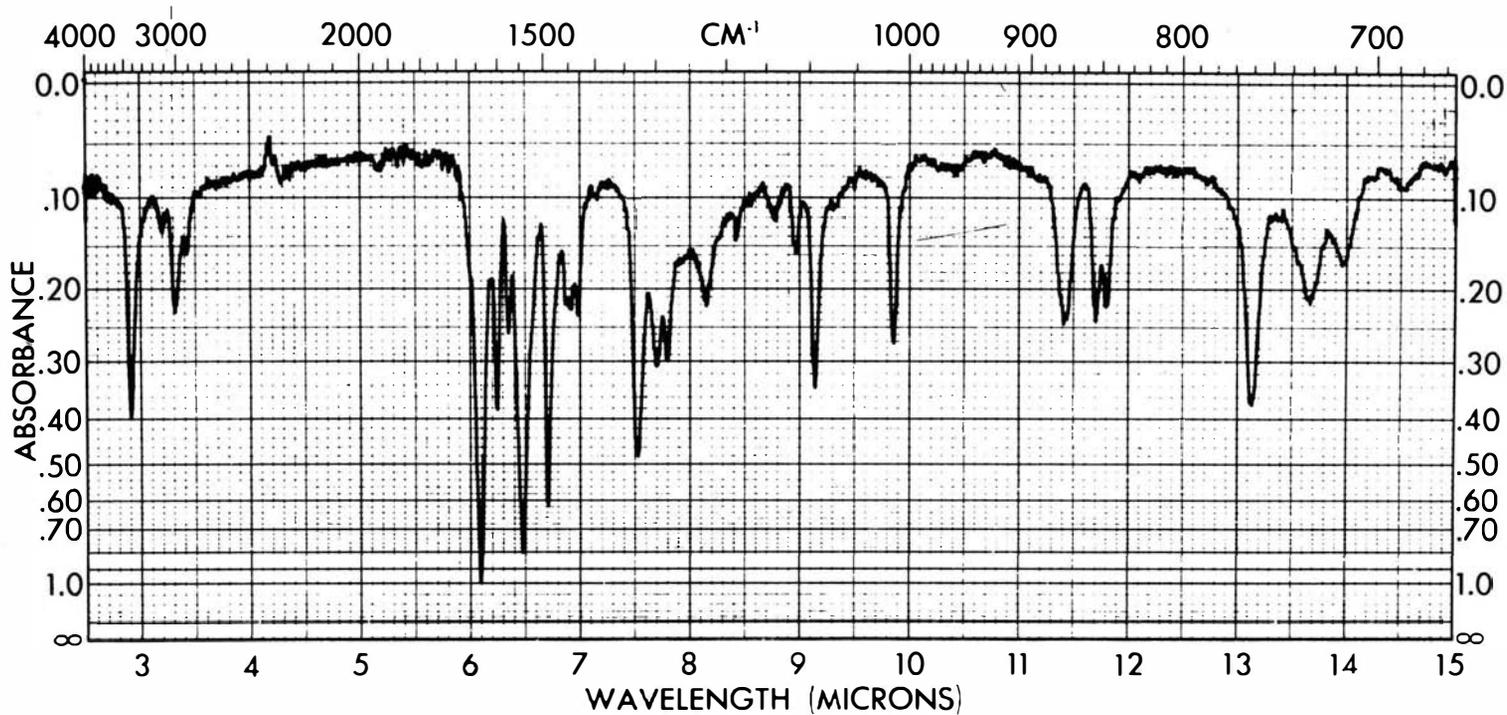
Samples of all the 2-oxazolines with the exception of the p-dimethylamino derivative were converted to the corresponding  $\beta$ -chloroamides by refluxing a solution of each in dioxane which had been previously saturated with

hydrogen chloride gas. The  $\beta$ -chloroamide structure was assigned to the conversion products on the basis of nitrogen analyses, infrared spectra, and physical properties. These compounds are insoluble in water, dilute acid and dilute base, but are soluble in ether. They give a positive halide test with alcoholic silver nitrate only when heated over a flame for 5 to 10 min. They all possess in their infrared spectra an amide carbonyl peak and a peak corresponding to an amide NH group. A typical spectrum is reproduced on page 31.

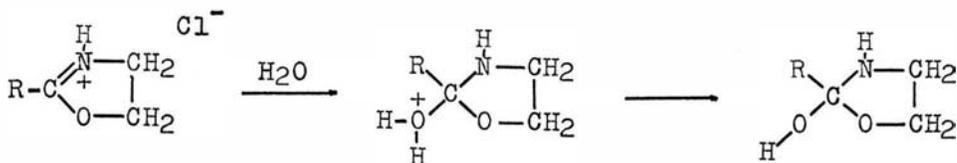
With the exception of the p-nitro derivative of which sufficient material was not available a sample of each chloroamide ( $X = -H, -Cl, -CH_3, \text{ or } -OEt$ ) was converted to the corresponding oxazoline by heating it in an alkaline medium for 3 min. The products so obtained were demonstrated to be identical with the products isolated from the thionyl chloride reactions by determination of mixture melting points and comparison of infrared spectra.

These 2-oxazoline compounds are insoluble in dilute base but are soluble in dilute acid. They can be alternately precipitated and redissolved by adjustment of the pH. 2-Oxazolines in general will hydrolyze to the corresponding  $\beta$ -acyloxyalkylamine salts in dilute acid. The mechanism of this hydrolysis (XLV) involves the attack of a water molecule at position "2" of the ring and subsequent ring opening (5) (52).

Of the members of this series, the p-nitro derivative was the most susceptible to acid hydrolysis. In fact, the



stability of this series of compounds to acid hydrolysis

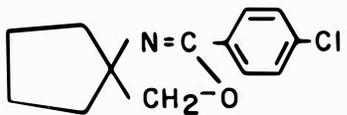
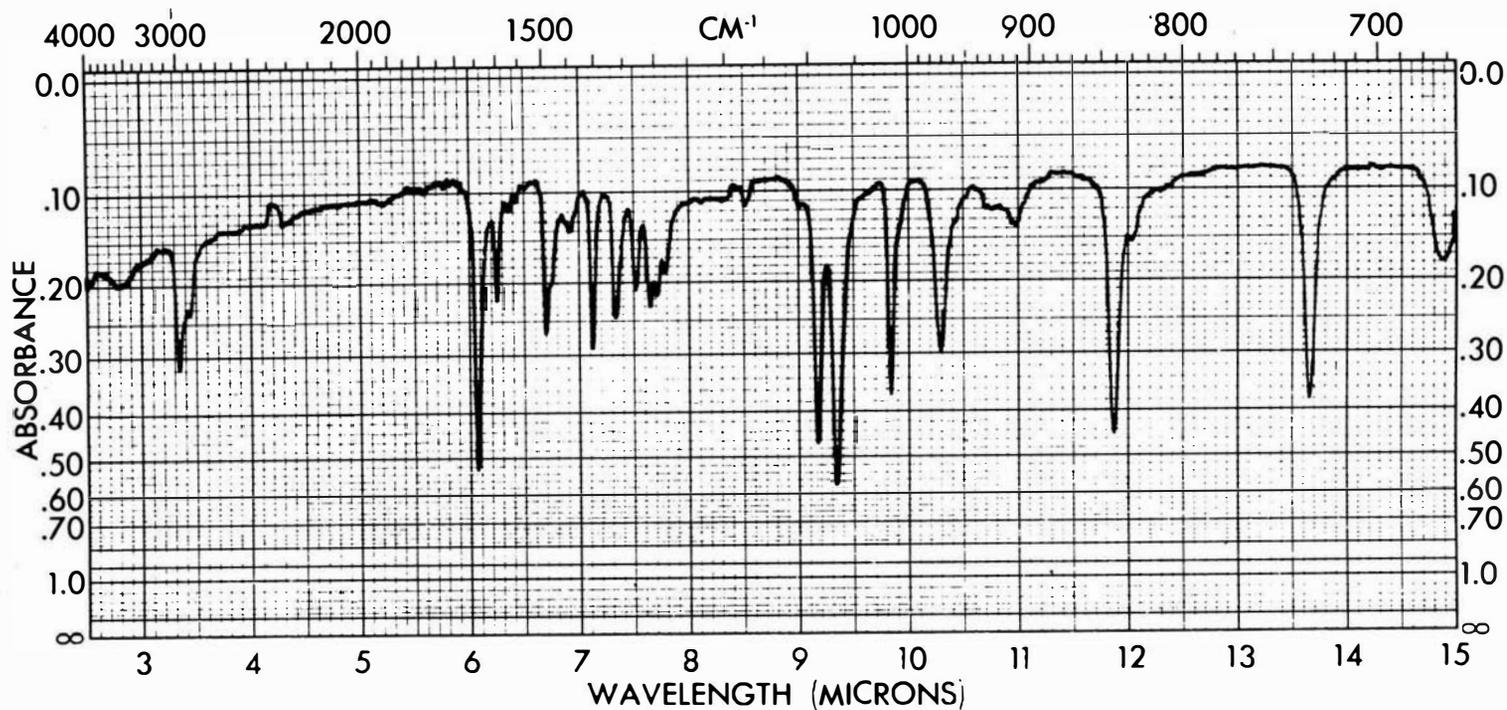


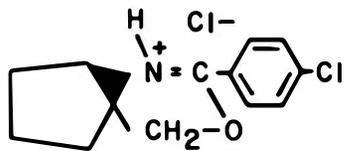
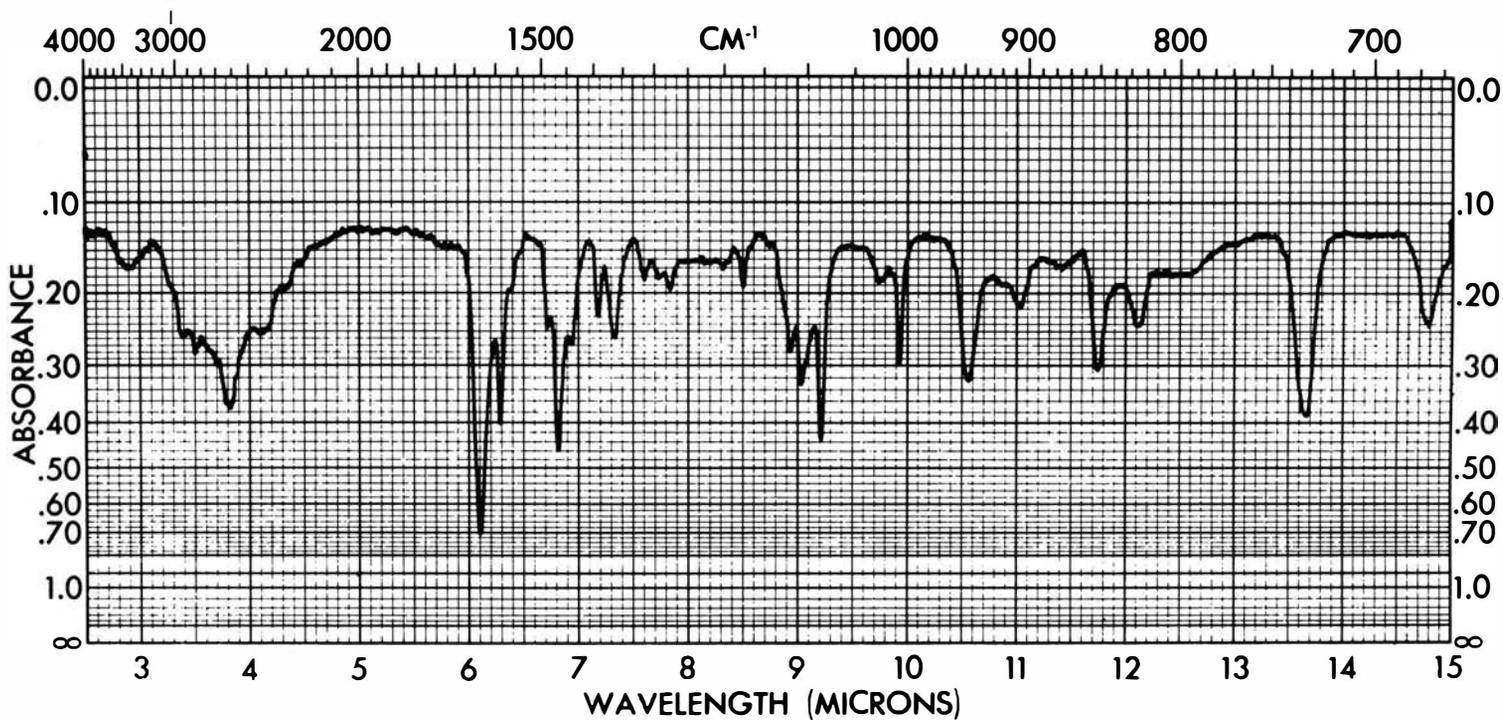
XLV



was observed, in general, to increase as the electron-donating ability of the p-substituent increased. However, it should be emphasized that this correlation is based on gross observations and not on kinetic data.

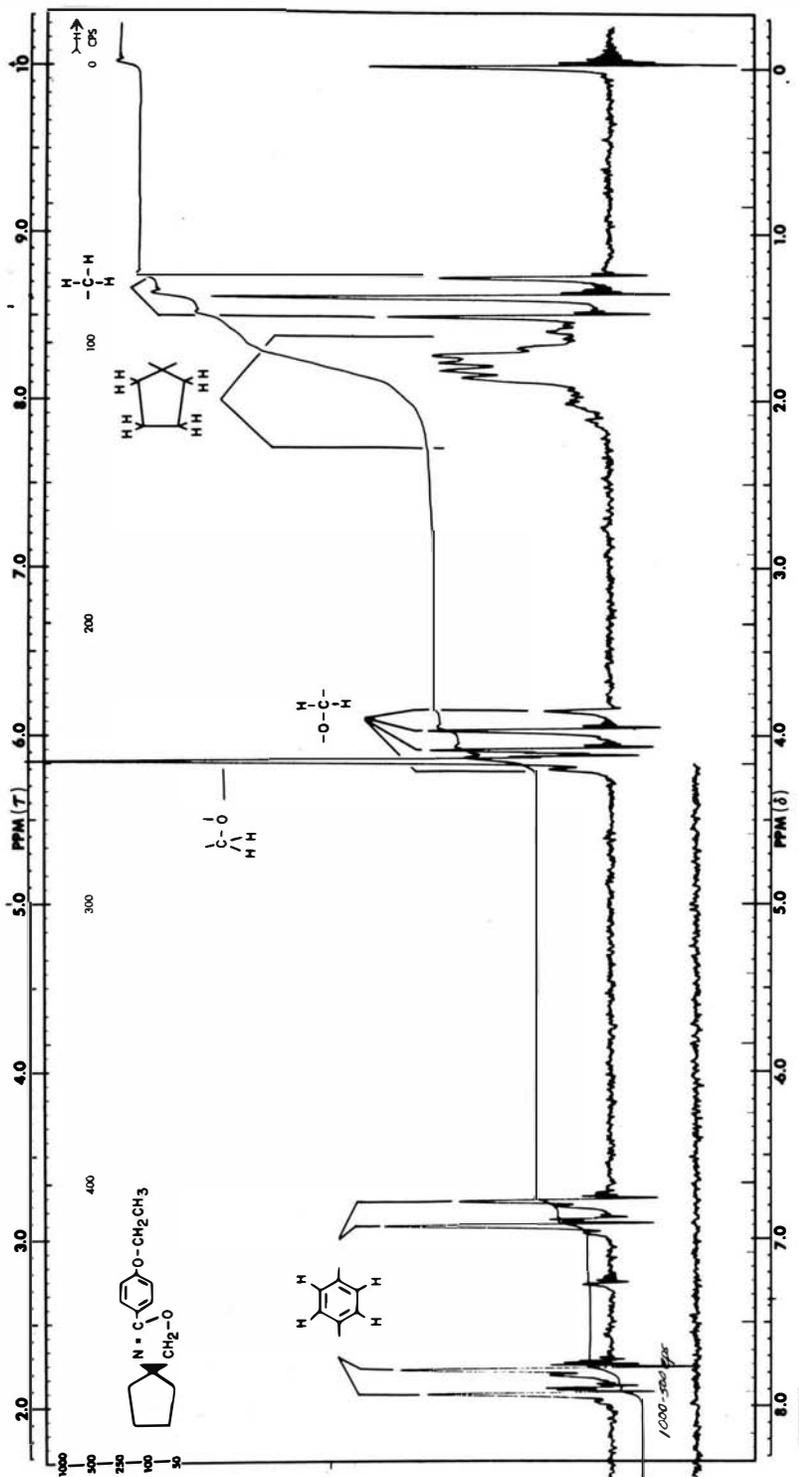
An infrared spectrum which is typical of those of the 2-oxazoline compounds of this series is reproduced on page 33. The infrared spectrum of the corresponding 2-oxazoline hydrochloride is reproduced on page 34. The principal features of both spectra are the presence of an absorption band near 6.1 microns ( $1640 \text{ cm}^{-1}$ ) and the absence of any absorption bands in the alcoholic OH and amide NH region (2.5 to 3.25 microns). The band near 6.1 microns corresponds to the imine group ( $\text{C}=\text{N}$ ) (2) of the oxazoline ring and in this series varies between 6.06 and 6.12 microns for the oxazolines and between 6.06 and 6.17 microns for the oxazoline hydrochlorides. The slight absorption present at 2.9 microns is due to the small amount of water in the potassium bromide powder from





which the compressed pellets of the samples to be analyzed are prepared. The absence of absorption between 2.5 and 3.25 microns is of major significance in the differentiation of the oxazoline structure from either the amido alcohol or the  $\beta$ -chloroamide structures both of whose infrared spectra ( pages 26 and 31 respectively) possess absorption peaks in this region. In addition to the imine band, the infrared spectra of the oxazoline hydrochlorides display a broad absorption band between 3.7 and 4.35 microns ( $2700$  and  $2300\text{ cm}^{-1}$ ) corresponding to the "ammonium" band of the  $\text{C}=\overset{+}{\text{N}}\text{H}$  group (2).

A proton magnetic resonance spectrum (p.m.r.) of 2-(p-ethoxyphenyl)-2-oxazoline-4-spirocyclopentane is reproduced on page 36. For each absorption band there is indicated on the spectrum the particular portion of the molecule responsible for the presence of that band. The areas under the absorption peaks are integrated, and their values are represented by a smooth line which is superimposed on the spectrum. The amount of increase in the height of this integration curve at a given absorption band is proportional to the number of protons which are in resonance at that particular tau ( $\tau$ ) value. The number of aromatic protons in 2-(p-ethoxyphenyl)-2-oxazoline-4-spirocyclopentane is known to be 4. By correlation of this fact with the height rise of the integration curve in the aromatic portion of the spectrum, the exact number of pro-



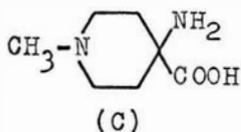
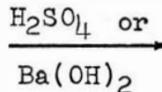
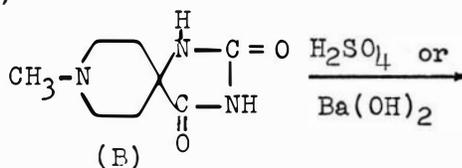
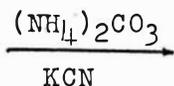
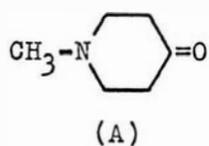
tons represented in each of the peaks of the spectrum can be calculated. Thus, there were found to be a total of 4 "etheric" protons and a total of 11 "alkyl" protons. The "etheric" group is composed of 2 protons of the oxazoline ring and 2 protons of the p-ethoxy group. The "alkyl" group is composed of 8 protons of the cyclopentane ring and 3 protons of the p-ethoxy group. Thus the 2-oxazoline structure of this compound is confirmed by its proton magnetic resonance spectrum.

The sequence of steps for the synthesis of the series of 1'-methyl-2-aryl-2-oxazoline-4-spiro-4'-piperidines is given in XLVI. The limitations of time restricted the syntheses in this series to two members, but it is felt that the feasibility of the synthetic route taken in this series is amply demonstrated.

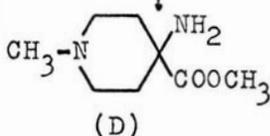
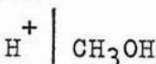
In XLVI the amino acid (C), which has not been reported in the literature, was prepared both by acidic ( $H_2SO_4$ ) and alkaline ( $Ba(OH)_2$ ) hydrolysis of the hydantoin (B). The products obtained from these two methods were shown to be the same by comparison of their infrared spectra.

The isolation of the amino acid from the acid hydrolysate proved to be difficult. No precipitation of amino acid sulfate occurred (as it had with the cyclopentane amino acid) upon cooling the reaction mixture to room temperature. The pH of a sample of the hydrolysate was adjusted with concentrated ammonium hydroxide consecutively to values of 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, and 10. The

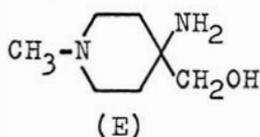
(XLVI)



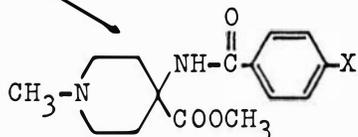
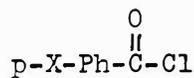
(C)



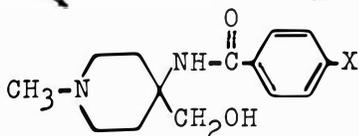
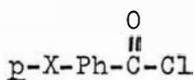
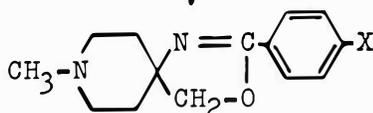
(D)



(E)



(F) (X = -H only)

(G) (X = -H or -CH<sub>3</sub>)

(H)

(X = -H or -CH<sub>3</sub>)

solution was refrigerated several hours at each value, but precipitation did not occur at any value. The isolation of the amino acid ( details of which are given on page 87 ) was accomplished by treatment of the acid hydrolysate with barium hydroxide, filtration of this suspension, treatment of the filtrate as needed with dilute solutions of barium hydroxide and sulfuric acid to remove completely both barium and sulfate ions, and evaporation of the filtrate to dryness under reduced pressure. The quantity of barium sulfate produced, the large volume of liquid handled, the numerous filtrations required, and the difficulty in removing completely both barium and sulfate ions from the solution made this procedure a long and tedious one. However, the high yield and purity of the amino acid obtained outweigh these disadvantages.

For preparation of larger quantities of the amino acid, the acid hydrolysis was preferred to the alkaline hydrolysis with barium hydroxide. Although the time of reaction was shorter, the yield slightly greater, and the work up procedure essentially the same in the alkaline hydrolysis, the acid hydrolysis was much more easily set up and required less attention during the reaction period.

The amino alcohol (E) was obtained by the reduction of the amino ester (D) with lithium borohydride. A complication not evident in the cyclopentane series was encountered in this reduction. The reduction of an ester with a borohydride results in the formation of a complex of

the alcohol which is produced and the boron containing radical remaining after the reduction. In the cyclopentane series this complex was broken up by water which was added after the reaction mixture had cooled to room temperature. When the same procedure was followed in the reduction of the 1-methylpiperidine amino ester (D), instead of the expected amino alcohol there was isolated a material which was assumed to be the reduction complex or a related structure on the basis of its wide melting range and its infrared spectrum. The infrared spectrum possessed a peak between 4.15 and 4.40 microns ( $2410$  and  $2273\text{ cm}^{-1}$ ), an area in which a BH group but very few other groups absorb radiation. A second peak corresponding to either a B-O or B-N structure was present between 8.4 and 8.6 microns ( $1190$  and  $1163\text{ cm}^{-1}$ ). The actual structure of this isolated complex is a matter of conjecture and may become the subject of future studies.

To decompose this complex a solution of the material in 10% hydrochloric acid was heated near boiling for 30 min., cooled, made alkaline, and extracted with tetrahydrofuran. The infrared spectrum of the material so obtained possessed essentially no absorption between 4.15 and 4.40 microns or between 8.4 and 8.6 microns. The melting range of the material had narrowed to  $145-146.5^{\circ}$ .

The same problem of a stable complex was encountered in the reduction of 4-benzamido-4-carbomethoxy-1-methylpiperidine (F) to the corresponding alcohol (G). In this case, as well as in subsequent reductions of 4-amino-4-

carbomethoxy-1-methylpiperidine, the complex was decomposed by acidifying and heating the reaction mixture prior to isolation of the product.

The preparation of 4-benzamido-4-carbomethoxy-1-methylpiperidine (F) was originally attempted by benzoylation of the amino ester (D) under Schotten-Baumann conditions. The white solid, which began to precipitate immediately upon addition of the benzoyl chloride and which was collected in sizable quantity at the end of the reaction, was found to be, not the expected product, but benzoic anhydride. Physical properties, the infrared spectrum, and other data (page 92) verify this structure assignment. Several modified procedures were tried in an effort to prevent the formation of the benzoic anhydride, but none was successful. In one experiment freshly distilled p-methylbenzoyl chloride was used in place of benzoyl chloride. The material which was isolated in good yield was identified as p-methylbenzoic anhydride on the basis of its melting point and infrared spectrum. This method was not pursued further, and no explanation can be offered for the formation of the anhydride in apparent preference to the amide.

The preparation of 4-benzamido-4-carbomethoxy-1-methylpiperidine (F) was accomplished by benzoylation of the amino ester (D) in dichloromethane with triethylamine as the base. Reduction of this amido ester (F) with lithium borohydride afforded the corresponding amido

alcohol (G in which X = -H). This compound was prepared also by the benzylation of the amino alcohol (E). The identity of these two products was established by the determination of a mixture melting point and by comparison of their infrared spectra. The p-methyl amido alcohol (G in which X = -CH<sub>3</sub>) was prepared only by acylation of the amino alcohol (E).

Both oxazolines (H) were prepared by treatment of the corresponding amido alcohols (G) with thionyl chloride. The infrared spectrum of each compound displays the characteristic imine peak.

## EXPERIMENTAL

General

All melting points were obtained with a Thomas-Hoover capillary melting point apparatus. They are uncorrected.

The elemental analyses denoted by a "T" were done by Triangle Chemical Laboratories, Chapel Hill, North Carolina. Those analyses designated by a "M" were done by Micro-Tech Laboratories, Skokie, Illinois. All other analyses were done at the Medical College of Virginia with a Coleman model 33 carbon-hydrogen analyzer and a Coleman model 29 nitrogen analyzer.

All infrared spectra were obtained with a Perkin-Elmer model 137 Infracord spectrophotometer. Unless otherwise stated, all samples were examined in the form of potassium bromide pellets.

The proton magnetic resonance spectrum of 2-(p-ethoxyphenyl)-2-oxazoline-4-spirocyclopentane was obtained with a Varian Associates model A 60 NMR Spectrometer through the courtesy of A. H. Robins Company, Richmond, Virginia.

Preparation of the  
Cyclopentane Series of 4-Spiro-2-aryl-2-oxazolines

Common Intermediates

Hydantoin-5-spirocyclopentane (1,3-diazaspiro(4.4)-nonane-2,4-dione). The following procedure is a modification of the method described by Hanze and Speer (53). Forty-two grams (0.5 m.) of cyclopentanone, 144 g. (1.5 m.) of ammonium carbonate and 65 g. (1.0 m.) of potassium cyanide were dissolved in 1250 ml. of 50% ethanol. This solution was placed in a two liter round-bottomed flask equipped with a magnetic stirrer and an air condenser. The reaction mixture was stirred at a temperature of 60-65° for 3 hrs. It was permitted to evaporate to approximately one half its volume and then was refrigerated for 12 hrs. The solid which precipitated was collected on a Büchner funnel, washed well with water, and recrystallized from 95% ethanol. The yield of pure material melting at 204-205° (lit. 204-205° (53)) was 64 g. (83%).

1-Aminocyclopentane-1-carboxylic Acid. The procedure of Goodson et al. (54) for the preparation of amino acids from hydantoins was followed with some modification. A solution of 62 g. (0.4 m.) of hydantoin-5-spirocyclopentane in 120 g. of sulfuric acid (1.2 m.) and 80 ml. of water was put in a 500 ml. round-bottomed flask which was

fitted with a water condenser and a magnetic stirrer. The solution was refluxed for 72 hrs. When the dark solution cooled to room temperature, the amino acid sulfate precipitated and was collected on a sintered glass funnel. The solid was dissolved in 125 ml. of water, and the resulting solution was decolorized with charcoal, filtered and adjusted to pH 6 with concentrated ammonium hydroxide. White crystals of the free amino acid precipitated from the warm solution, and further precipitation occurred on cooling. The acid filtrate from the original hydrolysis mixture was refrigerated overnight, and the amino acid sulfate which precipitated was treated in the manner described. After recrystallization from 75% ethanol, there was obtained a combined yield of 41 g. (79%) of product. The pure material, after 2 hrs. in an oven at 110°, melted at 332-333° dec. (lit. 328-329° dec. (55)).

l-Amino-l-carbomethoxycyclopentane Hydrochloride. The method employed is a modification of the procedure described by Connors and Ross (55). A suspension of 13 g. (0.1 m.) of l-aminocyclopentane-l-carboxylic acid in 300 ml. of methanol was placed in a three-necked, 500 ml. round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. The condenser was fitted with a calcium chloride drying tube to exclude moisture from the reaction. The flask was cooled in an ice bath while the suspension was saturated with hydrogen chloride gas. The reaction

mixture was then refluxed for 5 hrs. After 3 hrs., 25 ml. of 2,2-dimethoxypropane was added to the solution. At the end of the reflux period, the solution was evaporated under reduced pressure, and the thick oil which remained solidified upon addition of an acetone-ether mixture. After recrystallization from acetone-ethanol, 17 g. (94%) of product was obtained. The pure material melted at 205-207° (lit. 207-208° (55)).

p-Substituted Benzoyl Chlorides. The p-substituted benzoic acid (0.33 m.) was placed in a 300 ml. round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. A calcium chloride drying tube was attached to the condenser to exclude moisture from the reaction. Thionyl chloride (90 ml.) was added, and the mixture was refluxed until all the acid had dissolved and for one additional hour ( a total of about 4 hrs.). The thionyl chloride was removed under vacuum, and 30 ml. of benzene was added and removed under vacuum to free the reaction mixture of the last traces of thionyl chloride. The residue was distilled under reduced pressure to give the pure acid chloride.

2-Phenyl-2-oxazoline-4-spirocyclopentane

1-Benzamidocyclopentane-1-carboxylic Acid. The procedure followed is that described by Steiger (56) for the acylation of amino acids. To a one liter, three-necked round-bottomed flask equipped with a mechanical stirrer were added 43 g. (0.33 m.) of 1-aminocyclopentane-1-carboxylic acid and 165 ml. of 2 N sodium hydroxide. The flask was placed in an ice bath, and the solution was stirred vigorously while 40 ml. of benzoyl chloride and 165 ml. of 2 N sodium hydroxide were added from separate dropping funnels over a two hour period. The reaction mixture was stirred for two additional hours after all the reactants had been added. The solution was made acidic with 5 N hydrochloric acid, and the resulting precipitate was collected on a Büchner funnel. Recrystallization from 75% ethanol afforded 48 g. (62%) of product melting at 214-215° (lit. 214-215° (55)).

1-Benzamido-1-carbomethoxycyclopentane. Method I. The method employed is a modification of a procedure described by Loretto et al. (57) for the preparation of methyl esters utilizing 2,2-dimethoxypropane. Sixteen grams (0.07 m.) of 1-benzamidocyclopentane-1-carboxylic acid was dissolved in a mixture of 20 ml. of methanol, 50 ml. of 2,2-dimethoxypropane and 2 ml. of concentrated hydrochloric acid. The mixture was stirred for 30 hrs. at room temperature. The

reddish-brown solution was then evaporated to dryness. The residue was washed with dilute sodium hydroxide solution to remove unreacted acid, and then it was washed with ligroin to remove the color. Recrystallization from benzene-ligroin afforded 14 g. (83%) of product melting at 121.5-123°. The infrared spectrum shows the following absorption peaks: ester carbonyl: 5.77 microns ( $1733\text{ cm}^{-1}$ ); amide carbonyl: 6.14 microns ( $1629\text{ cm}^{-1}$ ); and amide NH: 2.96 microns ( $3378\text{ cm}^{-1}$ ).

Analysis:

Calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ :	C: 68.01%	H: 6.88%	N: 5.66%
Found:	68.11	7.18	5.39

Method II. To a 125 ml. Erlenmeyer flask equipped with a magnetic stirrer was added a solution of 9 g. (0.05 m.) of 1-amino-1-carbomethoxycyclopentane hydrochloride in 40 ml. of pyridine. Benzoyl chloride (7.0 g.) was added in portions to the stirred solution which was then heated to 100° for 20 min. After cooling to room temperature, the solution was diluted with 50 ml. of water and extracted with ether several times. The ether extracts were combined and washed successively with dilute hydrochloric acid and water. After drying over anhydrous sodium sulfate, the ether was evaporated leaving a residue of yellow solid. Recrystallization from ligroin afforded 7 g. (56%) of product melting at 121.5-123°. The identity of this compound with that from Method I was established by comparison of the infrared spectra (identical) and by a

mixture melting point (no depression).

1-Benzamido-1-hydroxymethylcyclopentane. In a 300 ml. round-bottomed flask equipped with a magnetic stirrer were placed 100 ml. of tetrahydrofuran and 2.2 g. (0.04 m.) of potassium borohydride. The flask was fitted with a reflux condenser which was equipped with a calcium chloride drying tube to exclude moisture from the reaction. The suspension was stirred at room temperature for 30 min. before 2.4 g. (0.055 m.) of anhydrous lithium chloride was added. The mixture was stirred for 8 hrs. at room temperature. A solution of 10 g. (0.04 m.) of 1-benzamido-1-carbomethoxycyclopentane in 25 ml. of tetrahydrofuran was added to the reaction mixture which was then refluxed for 10 hrs. After the mixture had cooled to room temperature, 25 ml. of water was added in portions to decompose the reduction complex and excess reducing agent. Upon addition of the water a two phase system formed. Stirring was continued for several hours until evolution of hydrogen was no longer evident. The tetrahydrofuran layer was removed in a separatory funnel, and the aqueous layer was extracted several times with tetrahydrofuran. The extracts and the original layer were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in a current of air. After recrystallization from benzene-ligroin, 7.3 g. (83%) of a white solid melting at 119-121° was obtained. The infrared spectrum clearly demonstrates that reduction of the ester occurred. Whereas the amide

carbonyl band is present at 6.14 microns ( $1629\text{ cm}^{-1}$ ), there is no band corresponding to an ester carbonyl function. Absorption peaks at 2.96 and 3.04 microns ( $3378$  and  $3289\text{ cm}^{-1}$ ) correspond to the NH and OH groups.

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_2$ :	C: 71.23%	H: 7.76%	N: 6.39%
Found:	71.18	7.96	6.42

1-Amino-1-cyclopentylmethyl Benzoate Hydrochloride by N - O Acyl Migration. A solution of 1-benzamido-1-hydroxymethylcyclopentane ( 1.0 g.) in 50 ml. of chloroform was saturated with hydrogen chloride gas and permitted to stand at room temperature in a stoppered flask for 24 hrs. Upon evaporation of the chloroform, there remained a solid which was washed with ether to remove any starting material present. Recrystallization of the crude material from acetone-ethanol afforded 0.88 g. (70%) of a water soluble compound which melted at  $230.5\text{-}231.5^\circ$  dec. The infrared spectrum supports the occurrence of nitrogen to oxygen acyl migration. Strong absorption due to the ammonium group is present in the region between 3.1 and 4.0 microns ( $3226$  and  $2500\text{ cm}^{-1}$ ); a peak at 5.80 microns ( $1724\text{ cm}^{-1}$ ) corresponding to an ester carbonyl group is also evident; no absorption occurs in the region corresponding to an amide carbonyl group.

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{18}\text{ClN}_2\text{O}$ :	C: 61.06%	H: 7.04%	N: 5.48%
Found:	60.93	7.30	5.53

1-Benzamido-1-hydroxymethylcyclopentane by O - N Acyl Migration. A solution of 0.5 g. of 1-amino-1-cyclopentylmethyl benzoate hydrochloride in 10 ml. of water was made distinctly alkaline with 1 N sodium hydroxide. The solution became cloudy immediately, and after 30 sec. a solid began to form. The solution was refrigerated for 1 hr. and then filtered. The solid which was collected was recrystallized from benzene-ligroin to give a pure compound melting at 119-120°. The identity of this material with authentic 1-benzamido-1-hydroxymethylcyclopentane ( page 49) was confirmed by comparison of the infrared spectra (identical) and by a mixture melting point (no depression).

2-Phenyl-2-oxazoline-4-spirocyclopentane (2-Phenyl-3-oxa-1-azaspiro(4.4)non-1-ene). Method I. This procedure is a modification of the method described by Winstein and Boschan (13) for the preparation of 2-oxazolines from amido alcohols. Five grams (0.023 m.) of 1-benzamido-1-hydroxymethylcyclopentane was added to a 125 ml. Erlenmeyer flask containing 20 ml. of benzene. Thionyl chloride (60 ml) was added in portions to the flask which during the addition was maintained at a temperature below 10° and shaken intermittently. The flask was stoppered and allowed to stand at room temperature for 24 hrs. The solution was then poured into 300 ml. of cold purified ether which was stirred vigorously during the addition. The white crystalline oxazoline hydrochloride precipitated immediately.

It was collected on a sintered glass funnel, washed well with purified ether, and recrystallized from dichloromethane-ether. There was obtained 5.1 g. (94%) of pure material melting at 135-136°. The infrared spectrum shows absorption maxima at 6.15 microns ( $1626\text{ cm}^{-1}$ ), corresponding to the imine group (C=N) of the oxazoline ring and between 3.70 and 4.35 microns ( $2700$  and  $2300\text{ cm}^{-1}$ ), corresponding to the "ammonium" band of the  $\text{C}=\text{NH}^+$  group.

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{16}\text{Cl NO}$ :	C: 65.68%	H: 6.74%	N: 5.91%
Found:	65.68	6.77	5.87

The free base was obtained by making distinctly alkaline with 1 N sodium hydroxide an aqueous solution of the oxazoline hydrochloride and extracting the resulting mixture with ether. The ether solution was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to leave a clear colorless liquid. The infrared spectrum (nujol) shows strong absorption at 6.08 microns ( $1645\text{ cm}^{-1}$ ) corresponding to the imine group. In order to obtain a crystalline derivative for analysis and further characterization, the picrate was prepared from a solution of the oxazoline base in 95% ethanol. After three recrystallizations from 95% ethanol, the material melted at 175-177°.

Analysis:

Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_8$ :	C: 53.02%	H: 4.16%	N: 13.02%
Found:	52.97	4.46	12.67

Method II. This procedure is essentially the same as that described by Boyd and Hansen (12) for preparation of substituted 2-phenyl-2-oxazolines from acylaminoalkanols. A solution of 2.2 g. (0.01 m.) of 1-benzamido-1-hydroxymethylcyclopentane in 8 ml. of pyridine was stirred and maintained at a temperature below 15° while 1.9 g. of p-toluenesulfonyl chloride was added dropwise. The solution was stoppered and allowed to stand at room temperature for 72 hrs. It then was poured into a cold mixture of 20 ml. of water and 8 ml. of concentrated hydrochloric acid, and the resulting solution was extracted with benzene to remove any unreacted or tosylated amido alcohol. The solution was made alkaline with 10% sodium hydroxide solution and extracted with ether. Removal of the ether under reduced pressure afforded a liquid residue which was dissolved in purified ether and the resulting solution treated with hydrogen chloride gas. The solid which precipitated was collected on a Büchner funnel and recrystallized from dichloromethane-ether. Less than 100 mg. of pure material melting at 134-136° was obtained.

The same procedure was repeated except the solution was held at 100° for 12 hrs. instead of at room temperature for 72 hrs. The solution was cooled and worked up in the manner previously described. Again, less than 100 mg. of material melting at 134-136° was obtained. The products from Methods I and II possess identical infrared spectra, and a mixture of the two products melts at 134-136°.

1-Benzamido-1-chloromethylcyclopentane. This method is a modification of the procedure described by Fry (5) for the general preparation of  $\beta$ -chloroalkylamides from 2-oxazolines. A solution of 2.3 g. of 2-phenyl-2-oxazoline-4-spirocyclopentane hydrochloride in 40 ml. of dioxane which had been saturated previously with hydrogen chloride gas was refluxed for 45 min. under anhydrous conditions. The solution was cooled and evaporated to dryness under reduced pressure. The solid residue was washed with water to remove water soluble material and then recrystallized from aqueous acetone to afford 1.8 g. (78%) of product. The pure compound melts at 126.5-127.5 $^{\circ}$ , is soluble in ether, and is insoluble in dilute acid or base. It gives a positive Beilstein test, but no precipitation occurs on treatment with alcoholic silver nitrate at room temperature. When this solution is heated for 5-10 min. over a flame, however, a precipitate of silver chloride slowly forms. The infrared spectrum shows a sharp band at 6.13 microns (1631  $\text{cm}^{-1}$ ) which corresponds to an amide carbonyl group. The spectrum also displays a sharp peak at 2.94 microns (3400  $\text{cm}^{-1}$ ) which is characteristic of the NH group. This data is in agreement with the characteristics of  $\beta$ -chloroalkylamides observed by van Tamelen (58).

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{16}\text{ClNO}$ :	C: 65.68%	H: 6.74%	N: 5.91%
Found:	65.48	6.89	5.71

2-Phenyl-2-oxazoline-4-spirocyclopentane from 1-Benzamido-1-chloromethylcyclopentane. The procedure employed is a modification of that described by Leffler and Adams (9) for the general synthesis of 2-oxazolines from  $\beta$ -chloroalkylamides. To 6 ml. of 70% ethanol containing 80 mg. of sodium hydroxide was added 300 mg. of 1-benzamido-1-chloromethylcyclopentane. The suspension was heated on a steam bath for 3 min. The chloroamide dissolved slowly as the solution became hot and was completely dissolved in 1 min. Immediately following the 3 min. reaction period, the solution was placed in an ice bath and diluted with 5 ml. of water. The solution was acidified with dilute hydrochloric acid and extracted with ether to remove unreacted starting material. The solution was made distinctly alkaline with 1 N sodium hydroxide and extracted several times with ether. The ether extracts were combined, dried over anhydrous sodium sulfate for 24 hrs. and filtered. Addition of hydrogen chloride gas to the ether solution caused the precipitation of a compound which afforded, after recrystallization from dichloromethane-ether, 200 mg. (67%) of pure material melting at 135-136°. The infrared spectrum of this compound is identical with that of authentic 2-phenyl-2-oxazoline-4-spirocyclopentane hydrochloride (page 52). There was no depression in the melting point of a mixture of the two compounds.

2-(p-Chlorophenyl)-2-oxazoline-4-spirocyclopentane1-(p-Chlorobenzamido)-cyclopentane-1-carboxylic Acid.

The procedure for the preparation of 1-benzamidocyclopentane-1-carboxylic acid was followed. Thirty-two grams (0.25 m.) of 1-aminocyclopentane-1-carboxylic acid was treated with 44 g. of p-chlorobenzoyl chloride and a total of 250 ml. of 2 N sodium hydroxide. The solid obtained on acidifying the reaction mixture was washed with ether to remove p-chlorobenzoic acid and recrystallized from 70% ethanol to give 30 g. (45%) of product. This material still contained some p-chlorobenzoic acid which was very difficult to remove completely. Rather than lose more material by further purification at this point, it was decided to eliminate the p-chlorobenzoic acid as its methyl ester in the following step.

1-(p-Chlorobenzamido)-1-carbomethoxycyclopentane. A

modified form of the method used to prepare 1-benzamido-1-carbomethoxycyclopentane was employed. Thirty grams (0.113 m.) of 1-(p-chlorobenzamido)-cyclopentane-1-carboxylic acid was dissolved in a mixture of 40 ml. of methanol, 100 ml. of 2,2-dimethoxypropane, and 4 ml. of concentrated hydrochloric acid. The solution was stirred at room temperature for 48 hrs. and then was evaporated to dryness. The solid residue was washed with petroleum ether to remove the red color. The methyl p-chlorobenzoate which

formed from the p-chlorobenzoic acid present in the starting material also was removed by the petroleum ether. The residue was suspended and stirred in dilute sodium hydroxide solution to remove unreacted starting material. The residue was then collected on a Büchner funnel, washed well with water, and recrystallized from aqueous acetone to afford 24 g. (82%) of product melting at 143-145°. The infrared spectrum shows absorption maxima at 5.84 microns ( $1712\text{ cm}^{-1}$ ) corresponding to an ester carbonyl group, 6.10 microns ( $1640\text{ cm}^{-1}$ ) corresponding to an amide carbonyl function, and 2.95 microns ( $3390\text{ cm}^{-1}$ ) corresponding to an amide NH group.

Analysis:

Calcd. for $\text{C}_{14}\text{H}_{16}\text{ClNO}_3$ :	C: 59.68%	H: 5.68%	N: 4.97%
Found:	60.06	6.19	5.08

1-(p-Chlorobenzamido)-1-hydroxymethylcyclopentane.

The procedure described for the reduction of 1-benzamido-1-carbomethoxycyclopentane to the corresponding alcohol was followed. Twenty-four grams (0.09 m.) of 1-(p-chlorobenzamido)-1-carbomethoxycyclopentane was treated with 5.4 g. of lithium chloride and 4.9 g. of potassium borohydride in 225 ml. of tetrahydrofuran. There was isolated, after recrystallization from 50% ethanol, 19.3 g. (85%) of product melting at 158-162°. An analytical sample, after two recrystallizations from benzene-ligroin, melted at 162-164.5°. The infrared spectrum exhibits peaks at 6.08

microns ( $1645\text{ cm}^{-1}$ ), 2.96 microns ( $3378\text{ cm}^{-1}$ ) and 2.86 microns ( $3497\text{ cm}^{-1}$ ). There is no absorption peak in the ester carbonyl region of the spectrum.

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{16}\text{ClNO}_2$ :	C: 61.53%	H: 6.31%	N: 5.52%
Found:	61.57	6.47	5.48

1-Amino-1-cyclopentylmethyl p-Chlorobenzoate Hydrochloride by N - O Acyl Migration. The procedure followed is essentially the same as that described for the preparation of 1-amino-1-cyclopentylmethyl benzoate hydrochloride. A solution of 1.5 g. of 1-(p-chlorobenzamido)-1-hydroxymethylcyclopentane in a mixture of 50 ml. of chloroform and 25 ml. of absolute ethanol was saturated with hydrogen chloride gas and allowed to stand at room temperature for 24 hrs. After evaporation of the solvent, the solid residue was washed with ether and recrystallized from ethanol-ether to give 1.25 g. (73%) of a water soluble compound melting at  $279.5\text{-}281^{\circ}$  dec. The infrared spectrum displays a broad ammonium band between 3.1 and 4 microns ( $3225$  and  $2500\text{ cm}^{-1}$ ) and an ester carbonyl band at 5.80 microns ( $1725\text{ cm}^{-1}$ ). There is essentially no absorption in the amide carbonyl region.

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{NO}_2$ :	C: 53.79%	H: 5.86%	N: 4.82%
Found:	53.99	6.18	4.81

1-(p-Chlorobenzamido)-1-hydroxymethylcyclopentane by O - N Acyl Migration. The procedure described for the conversion of 1-amino-1-cyclopentylmethyl benzoate hydrochloride to the corresponding amido alcohol was followed. A solution of 0.5 g. of 1-amino-1-cyclopentylmethyl p-chlorobenzoate hydrochloride in 10 ml. of water was made distinctly alkaline with 1 N sodium hydroxide. The solid which precipitated was recrystallized from benzene-ligroin to give a compound melting at 162-164.5°. The infrared spectrum of this compound is identical with that of authentic 1-(p-chlorobenzamido)-1-hydroxymethylcyclopentane (page 57). A mixture melting point of the two compounds was not depressed.

2-(p-Chlorophenyl)-2-oxazoline-4-spirocyclopentane (2-(p-Chlorophenyl)-3-oxa-1-azaspiro(4.4)non-1-ene). The procedure is essentially the same as that of Method I for the preparation of 2-phenyl-2-oxazoline-4-spirocyclopentane. Treatment of 2.5 g. (0.01 m.) of 1-(p-chlorobenzamido)-1-hydroxymethylcyclopentane with 10 ml. of benzene and 25 ml. of thionyl chloride afforded, after addition of purified ether (400 ml.) and petroleum ether (100 ml.), 2.2 g. (81%) of the oxazoline hydrochloride. Recrystallization from dichloromethane-ether gave a pure sample melting at 128.5-129.5°. The infrared spectrum (page 34) displays a band at 6.10 microns ( $1640\text{ cm}^{-1}$ ) corresponding to the imine function (C=N) of the oxazoline ring.

## Analysis:

Calcd. for $C_{13}H_{15}Cl_2NO$ :	C: 57.35%	H: 5.51%	N: 5.15%
Found:	57.20 T 57.34 M	5.97 T 5.65 M	5.21 T

The free base was precipitated from an aqueous solution of the oxazoline hydrochloride by addition of 1 N sodium hydroxide. The white solid was recrystallized twice from 50% ethanol to give a pure compound melting at 61-62°. The infrared spectrum (page 33) possesses the characteristic imine peak at 6.06 microns ( $1650\text{ cm}^{-1}$ ).

## Analysis:

Calcd. for $C_{13}H_{14}ClNO$ :	C: 66.24%	H: 5.95%	N: 5.95%
Found:	66.46 M	6.13 M	5.86

1-(p-Chlorobenzamido)-1-chloromethylcyclopentane. The procedure followed is essentially that described for the preparation of 1-benzamido-1-chloromethylcyclopentane. A solution of 1.0 g. of 2-(p-chlorophenyl)-2-oxazoline-4-spirocyclopentane in 40 ml. of dioxane, which had been saturated previously with hydrogen chloride gas, was refluxed for 45 min. The solution was cooled, and a solid precipitated. This precipitate was shown to be 1-amino-1-cyclopentylmethyl p-chlorobenzoate hydrochloride by comparison with an authentic sample (page 58). Such a side product in reactions of this type has been reported (5). The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. An aqueous

acetone solution of the residue was decolorized with charcoal and filtered. Addition of water caused a white solid to precipitate. Recrystallization of this solid from aqueous methanol yielded 650 mg. (65%) of pure material melting at 107-108°. The infrared spectrum (page 31) possesses an amide carbonyl band at 6.10 microns (1640  $\text{cm}^{-1}$ ) and a sharp NH peak at 2.91 microns (3436  $\text{cm}^{-1}$ ).  
 Analysis:

Calcd. for  $\text{C}_{13}\text{H}_{15}\text{Cl}_2\text{NO}$ : N: 5.15%

Found: 5.07

2-(p-Chlorophenyl)-2-oxazoline-4-spirocyclopentane  
from 1-(p-Chlorobenzamido)-1-chloromethylcyclopentane.

This method is essentially the same as that described for the conversion of 1-benzamido-1-chloromethylcyclopentane to 2-phenyl-2-oxazoline-4-spirocyclopentane. 1-(p-Chlorobenzamido)-1-chloromethylcyclopentane (300 mg.) was suspended in 6 ml. of 70% ethanol containing 80 mg. of sodium hydroxide. The suspension was heated on a steam bath for 3 min., cooled, diluted with 5 ml. of water, made acid, extracted with ether, and then made alkaline. A white solid precipitated which on recrystallization from aqueous acetone afforded 200 mg. (80%) of a pure compound melting at 61-62°. The infrared spectrum of this compound is identical with that of authentic 2-(p-chlorophenyl)-2-oxazoline-4-spirocyclopentane (page 59). The melting point of a mixture of the two compounds was not depressed.

2-(p-Methylphenyl)-2-oxazoline-4-spirocyclopentane1-(p-Methylbenzamido)-cyclopentane-1-carboxylic Acid.

This method is a modification of the procedure followed for the preparation of 1-benzamidocyclopentane-1-carboxylic acid. Thirty-two grams (0.25 m.) of 1-aminocyclopentane-1-carboxylic acid, 30 ml. of benzene, and 125 ml. of 2 N sodium hydroxide were placed in a one liter, three-necked round-bottomed flask equipped with a magnetic stirrer. The flask was placed in an ice bath, and the mixture was stirred vigorously while 125 ml. of 2 N sodium hydroxide and a solution of 39 g. of *p*-methylbenzoyl chloride in 50 ml. of benzene were added separately and slowly from dropping funnels over a 2 hr. period. After the additions were completed, the reaction mixture was stirred for 2 more hrs. The benzene layer was removed, and the aqueous layer was acidified with 10% hydrochloric acid to obtain the product. The material was air dried, washed with ether to remove *p*-methylbenzoic acid and recrystallized from 70% ethanol to give 16 g. (26%) of product. Just as in the case of the *p*-chloro derivative, a purification problem was encountered. *p*-Methylbenzoic acid was still present in the recrystallized product. This contaminant was removed as its methyl ester in the next step.

1-(p-Methylbenzamido)-1-carbomethoxycyclopentane. The procedure described for the synthesis of 1-(p-chlorobenzamido)-1-carbomethoxycyclopentane was followed. Sixteen grams (0.065 m.) of 1-(p-methylbenzamido)-cyclopentane-1-carboxylic acid was treated with 20 ml. of methanol, 50 ml. of 2,2-dimethoxypropane, and 2 ml. of concentrated hydrochloric acid. The residue remaining after evaporation of the reaction mixture was washed with petroleum ether to remove the methyl p-methylbenzoate formed from the p-methylbenzoic acid present in the starting material, and with 1 N sodium hydroxide to remove unreacted starting material. The residue was then recrystallized from aqueous acetone to give 10.5 g. (65%) of product. An analytical sample, after two recrystallizations from benzene-ligroin, melted at 117-119°. The infrared spectrum shows that both the amide and ester functions are present in the compound.

Analysis:

Calcd. for $C_{15}H_{19}NO_3$ :	C: 68.97%	H: 7.27%	N: 5.36%
Found:	68.85	7.29	5.32

1-(p-Methylbenzamido)-1-hydroxymethylcyclopentane.

The method employed was the same as that for the reduction of 1-benzamido-1-carbomethoxycyclopentane to the corresponding alcohol. 1-(p-Methylbenzamido)-1-carbomethoxycyclopentane (10.5 g., 0.04 m.) was treated with 2.2 g. of potassium borohydride and 2.4 g. of lithium chloride in 100 ml. of tetrahydrofuran. The reaction mixture yielded

7.0 g. (74%) of product which, after recrystallization from aqueous acetone, melted at 120-123°. An analytical sample, after two recrystallizations from benzene-ligroin, melted at 122.5-124.5°. The infrared spectrum possesses no absorption band in the ester carbonyl region.

Analysis:

Calcd. for $C_{14}H_{19}NO_2$ :	C: 72.10%	H: 8.15%	N: 6.01%
Found:	72.13	8.30	6.15

1-Amino-1-cyclopentylmethyl p-Methylbenzoate Hydrochloride by N - O Acyl Migration. The procedure employed in the preparation of 1-amino-1-cyclopentylmethyl p-chlorobenzoate hydrochloride was followed. Treatment of 1.5 g. of 1-(p-methylbenzamido)-1-hydroxymethylcyclopentane with a chloroform-ethanol mixture saturated with hydrogen chloride gas yielded 1.4 g. (80%) of a water soluble compound. After recrystallization from ethanol-ether the compound melted at 253.5-254.5° dec. The infrared spectrum possesses an ammonium band and an ester carbonyl band but does not show an amide carbonyl band.

Analysis:

Calcd. for $C_{14}H_{20}ClNO_2$ :	C: 62.34%	H: 7.42%	N: 5.19%
Found:	62.52	7.63	5.01

1-(p-Methylbenzamido)-1-hydroxymethylcyclopentane by O - N Acyl Migration. The procedure described for the conversion of 1-amino-1-cyclopentylmethyl benzoate hydrochloride

ride to the corresponding amido alcohol was followed. An aqueous solution of 1-amino-1-cyclopentylmethyl *p*-methylbenzoate hydrochloride was made distinctly alkaline with 1 N sodium hydroxide. The precipitate was recrystallized from benzene-ligroin to give a pure material melting at 122-124°. The infrared spectrum of this compound is identical with that of authentic 1-(*p*-methylbenzamido)-1-hydroxymethylcyclopentane (page 63). There was no depression in the melting point of a mixture of the two compounds.

2-(*p*-Methylphenyl)-2-oxazoline-4-spirocyclopentane  
(2-(*p*-Methylphenyl)-3-oxa-1-azaspiro(4.4)non-1-ene). The procedure described for the preparation of 2-phenyl-2-oxazoline-4-spirocyclopentane by Method I was followed. Treatment of 2.5 g. (0.01 m.) of 1-(*p*-methylbenzamido)-1-hydroxymethylcyclopentane with 10 ml. of benzene and 25 ml. of thionyl chloride afforded, on addition of purified ether, 1.8 g. (67%) of the oxazoline hydrochloride. A pure sample melting at 121.5-122.5° was obtained by recrystallization from dichloromethane-ether. The infrared spectrum shows an absorption peak at 6.17 microns ( $1621 \text{ cm}^{-1}$ ) which corresponds to the imine group (C=N).

Analysis:

Calcd. for $\text{C}_{14}\text{H}_{18}\text{ClNO}$ :	C: 66.80%	H: 7.16%	N: 5.57%
Found:	66.58 T	7.13 T	5.66 T

The free base was precipitated from a cold aqueous solution

of the hydrochloride by addition of 1 N sodium hydroxide. The solid was recrystallized from aqueous acetone to give a pure compound melting at 29.5-31°. The infrared spectrum displays the characteristic imine peak at 6.08 microns ( $1645\text{ cm}^{-1}$ ).

Analysis:

Calcd. for  $C_{14}H_{17}NO$ : N: 6.51%

Found: 6.49

1-(p-Methylbenzamido)-1-chloromethylcyclopentane. The procedure described for the preparation of 1-(p-chlorobenzamido)-1-chloromethylcyclopentane was followed. Treatment of 2-(p-methylphenyl)-2-oxazoline-4-spirocyclopentane (750 mg.) with 30 ml. of dioxane saturated with hydrogen chloride gas yielded, after recrystallization from aqueous acetone, 550 mg. (73%) of pure material melting at 100-101°. The infrared spectrum shows an amide band at 6.10 microns ( $1640\text{ cm}^{-1}$ ) and a sharp NH peak at 2.92 microns ( $3425\text{ cm}^{-1}$ ).

Analysis:

Calcd. for  $C_{14}H_{18}ClNO$ : N: 5.57%

Found: 5.50

2-(p-Methylphenyl)-2-oxazoline-4-spirocyclopentane from 1-(p-Methylbenzamido)-1-chloromethylcyclopentane. The procedure is the same as that described for the conversion of 1-benzamido-1-chloromethylcyclopentane to 2-phenyl-2-

oxazoline-4-spirocyclopentane. Treatment of 300 mg. of 1-(p-methylbenzamido)-1-chloromethylcyclopentane with 6 ml. of 70% ethanol and 80 mg. of sodium hydroxide yielded 175 mg. (58%) of product isolated as the hydrochloride. After recrystallization from dichloromethane-ether, the material melted at 120-121.5°. The infrared spectrum of this compound is identical with that of authentic 2-(p-methylphenyl)-2-oxazoline-4-spirocyclopentane hydrochloride (page 65). There was no depression in the melting point of a mixture of the two compounds.

2-(p-Nitrophenyl)-2-oxazoline-4-spirocyclopentane1-(p-Nitrobenzamido)-cyclopentane-1-carboxylic Acid.

The procedure followed is the same as that described for the preparation of 1-(p-methylbenzamido)-cyclopentane-1-carboxylic acid. Thirty-two grams (0.25 m.) of 1-aminocyclopentane-1-carboxylic acid was treated with 46.5 g. of p-nitrobenzoyl chloride and a total of 250 ml. of 2 N sodium hydroxide in the presence of 80 ml. of benzene. After removal of the benzene, the aqueous solution was acidified to obtain the product. This material was washed with ether and recrystallized from 70% ethanol to afford 40.0 g. (56%) of product which still contained p-nitrobenzoic acid. This contaminant was removed as its methyl ester in the following step.

1-(p-Nitrobenzamido)-1-carbomethoxycyclopentane. This procedure is the same as that employed for the preparation of 1-(p-chlorobenzamido)-1-carbomethoxycyclopentane. Forty grams (0.14 m.) of 1-(p-nitrobenzamido)-cyclopentane-1-carboxylic acid was treated with 50 ml. of methanol, 120 ml. of 2,2-dimethoxypropane, and 5 ml. of concentrated hydrochloric acid. The reaction mixture was evaporated to dryness and purified in the usual manner. The yield was 26 g. (62%). An analytical sample melting at 165.5-167° was obtained after three recrystallizations from benzene-ligroin. The infrared spectrum confirms the presence of

both the amide and ester linkages in the compound.

Analysis:

Calcd. for $C_{14}H_{16}N_2O_5$ :	C: 57.53%	H: 5.47%	N: 9.58%
Found:	57.46	5.68	9.43

1-(p-Nitrobenzamido)-1-hydroxymethylcyclopentane. The procedure described for the preparation of 1-benzamido-1-hydroxymethylcyclopentane was followed. Twenty-six grams (0.09 m.) of 1-(p-nitrobenzamido)-1-carbomethoxycyclopentane was treated with 5.4 g. of lithium chloride and 4.9 g. of potassium borohydride in 225 ml. of tetrahydrofuran. The reaction mixture was worked up in the usual manner. After recrystallization from benzene-ligroin, 16.5 g. (71%) of a yellow solid melting at 189-193° was obtained. A pure sample was obtained by decolorizing with charcoal a 95% ethanol solution of the material, filtering the solution, precipitating the solid by addition of water to the filtrate, and lastly, recrystallizing this solid twice from aqueous acetone. The pale yellow material thus obtained melted at 193.5-195°. The infrared spectrum shows no evidence of an ester carbonyl function.

Analysis:

Calcd. for $C_{13}H_{16}N_2O_4$ :	C: 59.09%	H: 6.10%	N: 10.61%
Found:	59.09	6.10	10.74

1-Amino-1-cyclopentylmethyl p-Nitrobenzoate Hydrochloride by N - O Acyl Migration. The procedure described for the preparation of 1-amino-1-cyclopentylmethyl p-chlorobenzoate hydrochloride was followed. Treatment of 1.5 g. of 1-(p-nitrobenzamido)-1-hydroxymethylcyclopentane with hydrogen chloride in a chloroform-ethanol mixture afforded 1.1 g. (65%) of a water soluble compound which, after recrystallization from ethanol-ether, melted at 245.5-246.5° dec. The infrared spectrum affirms the occurrence of nitrogen to oxygen acyl migration.

Analysis:

Calcd. for $C_{13}H_{17}ClN_2O_4$ :	C: 51.91%	H: 5.65%	N: 9.31%
Found:	51.67	5.95	9.36

1-(p-Nitrobenzamido)-1-hydroxymethylcyclopentane by O - N Acyl Migration. The procedure described for the conversion of 1-amino-1-cyclopentylmethyl benzoate hydrochloride to the corresponding amido alcohol was followed. An aqueous solution of 1-amino-1-cyclopentylmethyl p-nitrobenzoate hydrochloride was made distinctly alkaline with 1 N sodium hydroxide. The solid which precipitated was recrystallized from benzene-ligroin to give a pure compound melting at 193-195°. The infrared spectra (identical) and mixture melting point (no depression) confirm the identity of this compound with authentic 1-(p-nitrobenzamido)-1-hydroxymethylcyclopentane (page 69).

2-(p-Nitrophenyl)-2-oxazoline-4-spirocyclopentane

(2-(p-Nitrophenyl)-3-oxa-1-aza(4.4)non-1-ene). The procedure of Method I for the preparation of 2-phenyl-2-oxazoline-4-spirocyclopentane was followed essentially. Treatment of 2.5 g. (0.01 m.) of 1-(p-nitrobenzamido)-1-hydroxymethylcyclopentane with 10 ml. of benzene and 30 ml. of thionyl chloride afforded, after addition of purified ether-tetrahydrofuran (2:1 mixture), 2.4 g. (86%) of the oxazoline hydrochloride. Recrystallization from dichloromethane-ether gave pale yellow crystals melting at 120-121.5°. The infrared spectrum displays the imine band at 6.06 microns ( $1650 \text{ cm}^{-1}$ ).

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{O}_3$ :	C: 55.22%	H: 5.31%	N: 9.91%
Found:	55.57 M	5.38 M	10.04 M

The free base was prepared from an aqueous solution of the hydrochloride. The solution was decolorized with charcoal, filtered, and the filtrate made alkaline with 1 N sodium hydroxide. The precipitate was recrystallized from aqueous acetone to give a compound melting at 75-77°. The infrared spectrum shows an imine band at 6.12 microns ( $1634 \text{ cm}^{-1}$ ).

Analysis:

Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$ :	C: 63.41%	H: 5.69%	N: 11.38%
Found:	63.33 T	5.97 T	11.20 T

1-(p-Nitrobenzamido)-1-chloromethylcyclopentane. The procedure described for the preparation of 1-(p-chloro-benzamido)-1-chloromethylcyclopentane was followed. Treatment of 2-(p-nitrophenyl)-2-oxazoline-4-spirocyclopentane (100 mg.) with 25 ml. of dioxane saturated with hydrogen chloride gas yielded, after recrystallization from aqueous acetone, approximately 20 mg. (20%) of pure material melting at 147-149°. The infrared spectrum possesses an amide peak at 6.08 microns ( $1645\text{ cm}^{-1}$ ) and a sharp NH peak at 2.98 microns ( $3356\text{ cm}^{-1}$ ).

Analysis:

Calcd. for  $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{O}_3$ : N: 9.91%

Found: 9.60

2-(p-Ethoxyphenyl)-2-oxazoline-4-spirocyclopentane1-(p-Ethoxybenzamido)-cyclopentane-1-carboxylic Acid.

The procedure employed is the same as that described for the preparation of 1-benzamidocyclopentane-1-carboxylic acid. Thirty-two grams (0.25 m.) of 1-aminocyclopentane-1-carboxylic acid was treated with 46 g. of p-ethoxybenzoyl chloride and a total of 250 ml. of 2 N sodium hydroxide. There was obtained 15 g. (23%) of product after the crude material was washed with ether and recrystallized from 70% ethanol. p-Ethoxybenzoic acid was still present in the recrystallized material and was removed as its methyl ester in the next step.

1-(p-Ethoxybenzamido)-1-carbomethoxycyclopentane.

Method I. The procedure followed is the same as that given for the synthesis of 1-benzamido-1-carbomethoxycyclopentane. Fifteen grams (0.056 m.) of 1-(p-ethoxybenzamido)-cyclopentane-1-carboxylic acid was treated with 20 ml. of methanol, 50 ml. of 2,2-dimethoxypropane, and 2 ml. of concentrated hydrochloric acid. The residue remaining after evaporation of the solvent was purified in the usual manner to give 9.0 g. (56%) of product. After recrystallization from benzene-ligroin, the material melted at 122-123°. The infrared spectrum confirms the presence of both an ester and an amide function in the compound.

## Analysis:

Calcd. for $C_{16}H_{21}NO_4$ :	C: 65.95%	H: 7.21%	N: 4.81%
Found:	65.96	7.47	4.86

Method II. The method described by Ratouris and Behar (59) for the preparation of amides of amino acid esters was followed essentially in this procedure. To a solution of 15.0 g. (0.083 m.) of 1-amino-1-carbomethoxycyclopentane hydrochloride in 100 ml. of water was added 175 ml. of chloroform containing 16 g. of *p*-ethoxybenzoyl chloride. This reaction mixture was placed in a one liter volumetric flask and shaken on a mechanical shaking apparatus for 24 hrs. During this period, 16 g. (0.19 m.) of sodium bicarbonate was added to the mixture in portions. The chloroform layer was removed at the end of the reaction period, and the water layer was extracted several times with chloroform. The original chloroform layer and the extracts were combined, washed with dilute hydrochloric acid to remove unreacted starting material, washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The yellow residue was washed with ligroin to remove the color and recrystallized from benzene-ligroin to give 19 g. (79%) of product melting at 122-123°. The infrared spectra (identical) and mixture melting point (no depression) establish the identity of this product with that from Method I.

1-(p-Ethoxybenzamido)-1-hydroxymethylcyclopentane.

The same procedure as that described for the preparation of 1-benzamido-1-hydroxymethylcyclopentane was followed. Twenty grams (0.07 m.) of 1-(p-ethoxybenzamido)-1-carbomethoxycyclopentane was treated with 4.7 g. of lithium chloride and 4.3 g. of potassium borohydride in 200 ml. of tetrahydrofuran. The reaction mixture was worked up in the usual manner. After recrystallization from benzene-ligroin, 14 g. (76%) of product melting at 93-95° was obtained. Recrystallization from 60% ethanol afforded a pure sample melting at 94.5-95.5°. The infrared spectrum confirmed the complete reduction of the ester.

Analysis:

Calcd. for $C_{15}H_{21}NO_3$ :	C: 68.44%	H: 7.98%	N: 5.32%
Found:	68.27	7.97	5.45

1-Amino-1-cyclopentylmethyl p-Ethoxybenzoate Hydrochloride by N - O Acyl Migration. The procedure employed for the preparation of 1-amino-1-cyclopentylmethyl p-chlorobenzoate hydrochloride was followed. Treatment of 1.5 g. of 1-(p-ethoxybenzamido)-1-hydroxymethylcyclopentane with a chloroform and ethanol mixture saturated with hydrogen chloride gas yielded 1.2 g. (71%) of a water soluble compound which, after recrystallization from ethanol-ether, melted at 222-223° dec. The infrared spectrum confirms the occurrence of nitrogen to oxygen acyl migration.

## Analysis:

Calcd. for $C_{15}H_{22}ClNO_3$ :	C: 60.10%	H: 7.34%	N: 4.67%
Found:	60.12	7.75	4.48

1-(p-Ethoxybenzamido)-1-hydroxymethylcyclopentane by O - N Acyl Migration. The procedure described for the conversion of 1-amino-1-cyclopentylmethyl benzoate hydrochloride to the corresponding amido alcohol was followed. An aqueous solution of 1-amino-1-cyclopentylmethyl p-ethoxybenzoate hydrochloride was made distinctly alkaline with 1 N sodium hydroxide. The resulting precipitate was recrystallized from benzene-ligroin to give a pure sample melting at 94-95.5°. The infrared spectrum of this compound is identical with that of authentic 1-(p-ethoxybenzamido)-1-hydroxymethylcyclopentane (page 75). There was no depression in the melting point of a mixture of the two compounds.

2-(p-Ethoxyphenyl)-2-oxazoline-4-spirocyclopentane (2-(p-Ethoxyphenyl)-3-oxa-1-azaspiro(4.4)non-1-ene). The procedure for the preparation of 2-phenyl-2-oxazoline-4-spirocyclopentane by Method I was followed. Two grams (0.008 m.) of 1-(p-ethoxybenzamido)-1-hydroxymethylcyclopentane in 10 ml. of benzene was treated with 30 ml. of thionyl chloride. Upon addition of a 1:1 mixture of purified ether-petroleum ether, the oxazoline hydrochloride precipitated. The extremely hygroscopic nature of the

hydrochloride made its characterization virtually impossible. For this reason it was converted directly to the oxazoline. To obtain the oxazoline, an aqueous solution of the hydrochloride was decolorized with charcoal, filtered, and the base precipitated from the filtrate by addition of 1 N sodium hydroxide. After recrystallization from 50% ethanol, 1.15 g. (61%) of pure material melting at 80-81° was obtained. The infrared spectrum displays the imine absorption maximum at 6.10 microns (1640  $\text{cm}^{-1}$ ). The proton magnetic resonance spectrum (p.m.r.) ( page 36 ) in deuterated chloroform contains a triplet centered at 8.62  $\tau$  units ( $\tau$ ) ( $J = 7\text{cps.}$ ) corresponding to the " $\text{CH}_3$ " portion of the *p*-ethoxy substituent, a complex multiplet between 7.82 and 8.48  $\tau$  corresponding to the cyclopentane ring, a quartet centered at 5.96  $\tau$  ( $J = 7\text{ cps.}$ ) corresponding to the " $-\text{OCH}_2-$ " portion of the *p*-ethoxy substituent, a singlet at 5.84  $\tau$  corresponding to the " $-\text{OCH}_2-$ " group of the oxazoline ring, and a  $A_2B_2$  pattern centered at 2.63  $\tau$  ( $J = 7\text{ cps.}$ ) corresponding to the ring protons of the phenyl group. Integrated areas under the aromatic, etheric and alkyl absorption peaks were in the ratio: 4 : 4 : 11, in agreement with the assigned structure.

Analysis:

Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ :	C: 73.47%	H: 7.75%	N: 5.71%
Found:	73.28	7.98	5.74

1-(p-Ethoxybenzamido)-1-chloromethylcyclopentane. The procedure is the same as that given for the preparation of 1-(p-chlorobenzamido)-1-chloromethylcyclopentane. A solution of 400 mg. of 2-(p-ethoxyphenyl)-2-oxazoline-4-spirocyclopentane in 40 ml. of dioxane previously saturated with hydrogen chloride gas was refluxed for 45 min. and worked up in the usual manner. After recrystallization from aqueous acetone, a pure compound melting at 105-106° was obtained. The infrared spectrum displays an amide carbonyl band at 6.13 microns (1631  $\text{cm}^{-1}$ ) and a sharp NH peak at 2.95 microns (3390  $\text{cm}^{-1}$ )

Analysis:

Calcd. for  $\text{C}_{15}\text{H}_{20}\text{ClNO}_2$ : N: 4.97%

Found: 4.91

2-(p-Ethoxyphenyl)-2-oxazoline-4-spirocyclopentane  
from 1-(p-Ethoxybenzamido)-1-chloromethylcyclopentane.  
 The procedure followed is the same as that described for the conversion of 1-(p-chlorobenzamido)-1-chloromethylcyclopentane to 2-(p-chlorophenyl)-2-oxazoline-4-spirocyclopentane. Treatment of 100 mg. of 1-(p-ethoxybenzamido)-1-chloromethylcyclopentane with sodium hydroxide in 70% ethanol yielded 70 mg. (80%) of a compound melting at 80-81°. The infrared spectra (identical) and mixture melting point (no depression) establish the identity of this compound with authentic 2-(p-ethoxyphenyl)-2-oxazoline-4-spirocyclopentane (page 76).

2-(p-Dimethylaminophenyl)-2-oxazoline-4-spirocyclopentane

Attempted Preparation of 1-(p-Dimethylaminobenzamido)-1-carbomethoxycyclopentane by the Mixed Carbonic Anhydride Method. Attempts to prepare the desired compound by this method failed. In each case, however, there was isolated in good yield a compound whose properties, infrared spectrum, and elemental analysis strongly suggest it to be a p-dimethylaminobenzoic-carbonic anhydride. The procedure which was followed is a modification of the mixed anhydride method described by Vaughan and Osato (60) for the general preparation of peptides. A solution of 4.12 g. (0.025 m.) of p-dimethylaminobenzoic acid and 2.55 g. (0.025 m.) of triethylamine in 50 ml. of tetrahydrofuran was cooled to  $-5^{\circ}$  in an ice-salt bath. This solution was shaken intermittently while 2.7 g. (0.025 m.) of ethyl chlorocarbonate was added dropwise. Thirty minutes after the addition was completed, the solution was filtered to remove triethylamine hydrochloride. The filtrate was added in one portion to a stirred ice cold solution of 4.5 g. (0.025 m.) of 1-amino-1-carbomethoxycyclopentane hydrochloride and 2.55 g. (0.025 m.) of triethylamine in 100 ml. of chloroform. The reaction mixture was stirred for 2 hrs. in an ice bath and then was allowed to stand overnight at room temperature. The solution was evaporated to dryness under reduced pressure, and the residue was washed with dilute hydrochloric acid to remove unreacted starting materials and triethylamine hydrochloride. The solid which remained was not the

desired product, but, from all evidences, appeared to be a mixed carbonic anhydride of *p*-dimethylaminobenzoic acid.

An alternative procedure was tried which differs from the first method only in the solvent medium. The chloroform-triethylamine solution of 1-amino-1-carbomethoxycyclopentane hydrochloride was replaced by a solution of 4.5 g. of the amine ester hydrochloride and 2.0 g. (0.05 m) of sodium hydroxide in 30 ml. of water. The use of aqueous solutions in the mixed anhydride method has been described by Rinderknecht *et al.* (61). The reaction mixture was worked up exactly as described previously. The material isolated was identical with that from the first procedure.

A pure sample of the isolated solid was obtained by recrystallization from aqueous acetone. It has a melting point of 57-59°. It is insoluble in dilute acid or base but is very soluble in ether. The infrared spectrum of this compound displays carbonyl peaks at 5.55 microns ( $1802\text{ cm}^{-1}$ ) and 5.77 microns ( $1733\text{ cm}^{-1}$ ). The presence of two carbonyl peaks which are separated by 60 to 70  $\text{cm}^{-1}$  is characteristic of an anhydride structure (49). When concentrated hydrochloric acid was added to a sample of the compound in question, a vigorous and immediate evolution of gas occurred. The mixture was evaporated to dryness, and the residue was washed with ether and then recrystallized from 95% ethanol. The compound so obtained was proven to be identical with authentic *p*-dimethylaminobenzoic acid by comparison of the infrared spectra (identi-

cal) and by a mixture melting point (no depression) of the two compounds. The elemental analysis of the isolated anhydride supports the mixed carbonic anhydride structure assigned to it.

Analysis:

Calcd. for  $C_{12}H_{15}NO_4$ : C: 60.77% H: 6.33%

Found: 61.23 6.70

1-(p-Dimethylaminobenzamido)-1-carbomethoxycyclopentane. Dicyclohexylcarbodiimide Method. A modification of the procedure described by Diehl *et al.* (62) for the general preparation of peptides was employed. To a vigorously stirred suspension of 9.0 g. (0.05 m.) of 1-amino-1-carbomethoxycyclopentane in 500 ml. of dichloromethane were added successively 5.1 ml. (0.05 m.) of triethylamine, 8.25 g. (0.05 m.) of *p*-dimethylaminobenzoic acid and 10.5 g. (0.055 m.) of dicyclohexylcarbodiimide. The reaction mixture was then stirred for 48 hrs. at room temperature. At the end of the reaction period, the suspension was filtered to remove dicyclohexylurea, and the filtrate was evaporated to dryness. The residue was washed with several portions of 1 N hydrochloric acid, and the acid solutions were combined, decolorized with charcoal, and filtered. The filtrate was made distinctly alkaline with 2 N sodium hydroxide, and the resulting precipitate was collected on a Büchner funnel and washed well with water. Recrystallization from 50% ethanol afforded 9.5 g. (65%) of product

melting at 154.5-156°. The infrared spectrum displays both an ester and an amide carbonyl band.

Analysis:

Calcd. for $C_{16}H_{22}N_2O_3$ :	C: 66.21%	H: 7.59%	N: 9.65%
Found:	66.10	7.73	9.60

The hydrochloride was prepared from an ether solution of the base by bubbling in hydrogen chloride gas. It melts at 188.5-191.5° dec.

Analysis:

Calcd. for $C_{16}H_{23}ClN_2O_3$ :	C: 58.81%	H: 7.04%	N: 8.57%
Found:	58.83	7.73	8.56

1-(p-Dimethylaminobenzamido)-1-hydroxymethylcyclopentane. The procedure used for the preparation of 1-benzamido-1-hydroxymethylcyclopentane was followed. Treatment of 5.5 g. (0.02 m.) of 1-(p-dimethylaminobenzamido)-1-carbomethoxycyclopentane with 1.1 g. of potassium borohydride and 1.2 g. of lithium chloride in 50 ml. of tetrahydrofuran afforded 4.1 g. (82%) of product. After recrystallization from 50% ethanol and then benzene-petroleum ether, a pure sample melting at 133-134.5° was obtained. The infrared spectrum displays no absorption band in the ester carbonyl region.

Analysis:

Calcd. for $C_{15}H_{22}N_2O_2$ :	C: 68.70%	H: 8.39%	N: 10.67%
Found:	68.80	8.72	10.81

The hydrochloride was prepared from an ethanol-ether solu-

tion of the base by bubbling in hydrogen chloride gas. After recrystallization from ethanol-ether, it melted at 160-162°.

Analysis:

Calcd. for  $C_{15}H_{23}ClN_2O_2$ : N: 9.38%

Found: 9.21

1-Amino-1-cyclopentylmethyl p-Dimethylaminobenzoate Dihydrochloride by N - O Acyl Migration. The method employed is essentially that described for the preparation of 1-amino-1-cyclopentylmethyl benzoate hydrochloride. Two grams (0.008 m.) of 1-(p-dimethylaminobenzamido)-1-hydroxymethylcyclopentane was dissolved in 35 ml. of absolute ethanol. The solution was saturated with hydrogen chloride gas and allowed to stand at room temperature for 20 hrs. Purified ether was added to precipitate a compound melting at 227-232° dec. The material was recrystallized from ethanol-ether to give a pure compound melting at 240-241.5°. The infrared spectrum confirms the occurrence of nitrogen to oxygen acyl migration.

Analysis:

Calcd. for  $C_{15}H_{24}Cl_2N_2O_2$ : N: 8.36%

Found: 8.21

1-(p-Dimethylaminobenzamido)-1-hydroxymethylcyclopentane by O - N Acyl Migration. The procedure used is the same as that described for the conversion of 1-amino-1-

cyclopentylmethyl benzoate hydrochloride to the corresponding alcohol. Treatment of an aqueous solution of 1-amino-1-cyclopentylmethyl p-dimethylaminobenzoate dihydrochloride with 1 N sodium hydroxide afforded a compound which melted at 132-134<sup>o</sup>. This compound was shown to be identical with authentic 1-(p-dimethylaminobenzamido)-1-hydroxymethylcyclopentane (page 82) by comparison of their infrared spectra (identical) and determination of a mixture melting point (no depression).

2-(p-Dimethylaminophenyl)-2-oxazoline-4-spirocyclopentane (2-(p-Dimethylaminophenyl)-3-oxa-1-azaspiro(4.4)-non-1-ene). The procedure described for the preparation of 2-phenyl-2-oxazoline-4-spirocyclopentane by Method I was followed. Two grams (0.076 m.) of 1-(p-dimethylaminobenzamido)-1-hydroxymethylcyclopentane was treated with 10 ml. of benzene and 30 ml. of thionyl chloride. Upon addition of purified ether to the reaction mixture, a yellow solid precipitated (presumed to be the dihydrochloride of the oxazoline) and was immediately dissolved in 10 ml. of water. The solution was decolorized with charcoal, filtered, and made alkaline with 1 N sodium hydroxide. The solid which precipitated was collected on a sintered glass funnel, washed well with water, and recrystallized from aqueous acetone. There was obtained 1.85 g. (82%) of product melting at 108-110<sup>o</sup>. The infrared spectrum possesses the characteristic imine band at 6.10

microns ( $1640\text{ cm}^{-1}$ ).

**Analysis:**

Calcd. for  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}$ : C: 73.77% H: 8.88% N: 11.47%

Found:	73.93 M	8.42 M	11.67 M
	73.82 M	8.31 M	11.24

Attempts to prepare the dihydrochloride led only to a product having an indefinite melting point. No further attempts were made to characterize this material.

Preparation of the  
1-Methylpiperidine Series of 4-Spiro-2-aryl-2-oxazolines

Common Intermediates

1-Methylpiperidine-4-spiro-5'-hydantoin (8-Methyl-1,3,8-triazaspiro(4.5)decane-2,4-dione). The procedure is essentially the same as that given for the preparation of hydantoin-5-spirocyclopentane (page 44). A solution of 160 g. (1.4 m.) of N-methyl-4-piperidone, 395 g. of ammonium carbonate, and 182 g. of potassium cyanide in 3500 ml. of 60% ethanol was stirred for 8 hrs. at a temperature of 60-65°. After 4 hrs. an additional 100 g. of ammonium carbonate and 40 g. of potassium cyanide were added to the reaction mixture. At the end of the reaction period the solution was permitted to evaporate to about one half its volume and then was refrigerated 12 hrs. The solid which precipitated was collected on a Büchner funnel and suspended in approximately 300 ml. of water. The suspension was stirred vigorously for 10-15 min. and then filtered. The solid which was collected was washed with an additional 100 ml. of water and air dried overnight. There was obtained 147 g. (56%) of product. An analytical sample, which was obtained after two recrystallizations from 95% ethanol, melted at 280-282° dec. (sealed tube) (lit. 254-256° (63)). No explanation can be offered for the difference in the melting point of this material and

the melting point reported in the literature. The value of 280-282° was observed with samples from several reaction mixtures.

**Analysis:**

Calcd. for $C_8H_{13}N_3O_2$ :	C: 52.45%	H: 7.15%	N: 22.94%
Found:	51.92	6.87	22.94

4-Amino-1-methylpiperidine-4-carboxylic Acid. Method I.

Acid Hydrolysis. The method employed is a modification of the procedure for the preparation of 1-aminocyclopentane-1-carboxylic acid (page 44). A solution of 100 g. (0.55 m.) of 1-methylpiperidine-4-spiro-5'-hydantoin in 275 g. of 60% sulfuric acid was refluxed with stirring for 120 hrs. After cooling to room temperature, the reaction mixture was made distinctly alkaline by addition of an aqueous solution of barium hydroxide in portions. The mixture was filtered several times during the neutralization to remove the precipitated barium sulfate. After an excess of barium hydroxide had been added, the mixture was gently boiled with stirring for 30 min. to remove the ammonia which had formed as a by-product of the hydrolysis and to digest the barium sulfate precipitate. The mixture was cooled and filtered. The filtrate was treated with dilute sulfuric acid until no more barium sulfate precipitated, gently boiled for 30 min., and filtered. The clear filtrate was evaporated to one third its volume under reduced pressure. Samples of this concentrated solution were tested

for the presence of barium and sulfate ions with dilute solutions of sulfuric acid and barium chloride. The concentrated filtrate then was treated as needed with dilute sulfuric acid or barium hydroxide solution until it was free of both barium and sulfate ions. It was then evaporated to dryness under reduced pressure. The residue was dissolved in a 1:1 mixture of methanol and ethanol, and the resulting solution was filtered. The filtrate was evaporated to dryness to yield 64 g. (74%) of amino acid. An analytical sample melting at 275-276° dec. (sealed tube) was obtained after two recrystallizations from 95% ethanol. The infrared spectrum shows typical amino acid absorption. Strong absorption between 3.0 and 4.0 microns (3330 and 2500  $\text{cm}^{-1}$ ) corresponding to the ammonium group is present. Also, strong absorption occurs between 5.9 and 6.7 microns (1700 and 1490  $\text{cm}^{-1}$ ) corresponding to the carboxylate group.

Analysis:

Calcd. for $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2$ :	C: 53.15%	H: 8.92%	N: 17.71%
Found:	53.51 M	9.01 M	17.36 M 17.74

Method II. Alkaline Hydrolysis. To a hot, stirred suspension of 90 g. of barium hydroxide in 90 ml. of water was added in portions 18 g. (0.1 m.) of 1-methylpiperidine-4-spiro-5'-hydantoin. The mixture was refluxed for 72 hrs, cooled, and filtered. The filtrate was treated with 20% sulfuric acid until no more barium sulfate precipitated. The filtrate was then boiled gently for 30 min. and filtered.

Samples of this filtrate were tested for the presence of barium and sulfate ions, and the filtrate was treated as needed with dilute solutions of sulfuric acid or barium hydroxide until it was free of barium and sulfate ions. The solution was evaporated to dryness under reduced pressure to give 12.5 g. (80%) of amino acid melting at 274-275° dec. (sealed tube). The infrared spectrum of this product is identical with that of the product from Method I.

4-Amino-4-carbomethoxy-1-methylpiperidine. The procedure is essentially the same as that for the preparation of 1-amino-1-carbomethoxycyclopentane hydrochloride (page 45). A suspension of 55 g. (0.35 m.) of 4-amino-1-methylpiperidine-4-carboxylic acid in 1200 ml. of methanol was saturated with hydrogen chloride gas and refluxed for 6 hrs. to afford 83 g. (97%) of the ester dihydrochloride. The melting range of this material was very wide and repeated recrystallizations did not narrow the range appreciably. This wide melting range is most probably due to the presence of small amounts of both unreacted amino acid and the monohydrochloride of the ester. The infrared spectrum possesses a peak at 5.77 microns ( $1733\text{ cm}^{-1}$ ) which is characteristic of an ester carbonyl group. The ester was not further characterized as its dihydrochloride.

The free base was prepared by addition of triethylamine to a suspension of the finely divided dihydrochloride in dichloromethane. After addition of the triethylamine, the

suspension was filtered to remove any unreacted amino acid present and then was evaporated to dryness under reduced pressure. The residue was washed with ether, and the resulting ether solution was filtered. The ether and any excess triethylamine were removed on a rotatory evaporator at a temperature of 50° to afford the liquid amino ester. The procedure of washing with ether, filtering, et cet. was repeated once to insure the purity of the amino ester. The infrared spectrum (nujol) of the liquid displays the characteristic ester carbonyl band at 5.76 microns. An analytical sample was dried in a vacuum desiccator over calcium chloride for 48 hrs.

Analysis:

Calcd. for  $C_8H_{16}N_2O_2$ : N: 16.27%

Found: 15.85

4-Amino-4-hydroxymethyl-1-methylpiperidine. The procedure for the preparation of 1-benzamido-1-hydroxymethylcyclopentane (page 49) was followed with some modification. A mixture of 7.0 g. (0.04 m.) of 4-amino-4-carbomethoxy-1-methylpiperidine, 2.7 g. (0.05 m.) of potassium borohydride, and 3.0 g. (0.07 m.) of lithium chloride in 100 ml. of tetrahydrofuran was refluxed for 12 hrs. Upon cooling to room temperature, the mixture was treated with 10 ml. of water and stirred for 8 hrs. To insure the complete decomposition of the reduction complex (see page 40), concentrated hydrochloric acid was added cautiously until the

mixture was distinctly acid. The mixture was stirred under a condenser at  $60^{\circ}$  for 8 hrs., cooled, and made distinctly alkaline with 20% sodium hydroxide solution. The tetrahydrofuran layer was removed, and the water layer was extracted several times with tetrahydrofuran. The original tetrahydrofuran layer and the extracts were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated to dryness on a rotatory evaporator. The viscous liquid which remained solidified upon addition of ether. The solid was collected on a filter, washed with ether, and recrystallized from benzene to afford 3.9 g. (58%) of product melting at  $145-146.5^{\circ}$ . The infrared spectrum displays absorption maxima at 2.93 microns ( $3413\text{ cm}^{-1}$ ), 3.07 microns ( $3257\text{ cm}^{-1}$ ) and 6.07 microns ( $1647\text{ cm}^{-1}$ ). There is no absorption in the ester carbonyl region of the spectrum.

Analysis:

Calcd. for $\text{C}_7\text{H}_{16}\text{N}_2\text{O}$ :	C: 58.30%	H: 11.18%	N: 19.43%
Found:	58.94	9.75	19.26

1'-Methyl-2-phenyl-2-oxazoline-4-spiro-4'-piperidine

Attempted Preparation of 4-Benzamido-4-carbomethoxy-1-methylpiperidine. Benzoyl chloride (9.5 ml.) was added dropwise over a two hour period to a cold, vigorously stirred solution of 20 g. (0.08 m.) of 4-amino-4-carbomethoxy-1-methylpiperidine dihydrochloride and 20 g. of monohydrated sodium carbonate (0.16 m.) in 45 ml. of water. A white solid began to precipitate almost immediately upon addition of the benzoyl chloride. The reaction mixture was stirred for 2 hrs. after the addition was completed and then was diluted with 50 ml. of water and filtered. The white solid which was collected was washed well with water and air dried. This material was shown to be benzoic anhydride instead of the expected product. The material is insoluble in dilute acid or base but is soluble in ether. It melts at 40-42° (lit. value for benzoic anhydride is 42° (64)). The infrared spectrum is essentially identical with that of an authentic sample of benzoic anhydride. Acid hydrolysis of a 0.469 g. sample of the material yielded 0.429 g. of benzoic acid. This amount is more than twice the theoretical amount (0.207 g.) of benzoic acid which the sample would yield if it were the benzamide of 4-amino-4-carbomethoxy-1-methylpiperidine. This quantity is only slightly less than the theoretical amount (0.504 g.) which the sample would yield if it were benzoic anhydride.

The same procedure was repeated several times using freshly distilled benzoyl chloride. Sodium bicarbonate and sodium hydroxide were each tried in place of sodium carbonate. One attempt was made at room temperature with sodium hydroxide as the base. The results were the same in each case; benzoic anhydride formed instead of the desired product.

4-Benzamido-4-carbomethoxy-1-methylpiperidine. A solution of 2.8 g. of benzoyl chloride in 30 ml. of dichloromethane was added dropwise over a two hour period to a vigorously stirred solution of 3.4 g. (0.02 m.) of 4-amino-4-carbomethoxy-1-methylpiperidine and 2.5 g. (0.025 m.) of triethylamine in 150 ml. of dichloromethane. The solution was stirred for 12 hrs. at room temperature after the addition was completed. It was then evaporated to dryness under reduced pressure. The residue was washed several times with benzene, and the benzene solutions were combined and evaporated to dryness under reduced pressure. There remained a gum which solidified upon addition of ether. The solid was collected on a Büchner funnel, washed with more ether, and recrystallized from benzene-petroleum ether to afford 1.35 g. (24%) of product melting at 127-128.5°. The infrared spectrum displays absorption bands at 2.98 microns ( $3355\text{ cm}^{-1}$ ) corresponding to an NH group, at 5.75 microns ( $1739\text{ cm}^{-1}$ ) corresponding to an ester carbonyl group, and at 6.09 microns ( $1642\text{ cm}^{-1}$ )

corresponding to an amide carbonyl group.

**Analysis:**

Calcd. for  $C_{15}H_{20}N_2O_3$ : N: 10.14%

Found: 9.93

4-Benzamido-4-hydroxymethyl-1-methylpiperidine from 4-Amino-4-hydroxymethyl-1-methylpiperidine. A mixture of 35 ml. of chloroform and a solution of 3.0 g. (0.02 m.) of 4-amino-4-hydroxymethyl-1-methylpiperidine and 1.0 g. of sodium hydroxide in 25 ml. of water was stirred vigorously at room temperature while a solution of 2.8 g. of benzoyl chloride in 15 ml. of chloroform was added dropwise over a two hour period. The reaction mixture was stirred for 12 hrs. after the addition was completed. The chloroform layer was removed, and the water layer was extracted several times with chloroform. These extracts and the original chloroform layer were combined and evaporated to dryness in a stream of air. The solid residue was washed consecutively with ether and water, air dried, and recrystallized from tetrahydrofuran-acetone to give 2.0 g. (40%) of product melting at 196-198<sup>o</sup> dec. The infrared spectrum possesses a sharp NH peak at 3.0 microns ( $3333\text{ cm}^{-1}$ ), an OH peak at 3.12 microns ( $3205\text{ cm}^{-1}$ ), and an amide carbonyl peak at 6.09 microns ( $1642\text{ cm}^{-1}$ ).

**Analysis:**

Calcd. for  $C_{14}H_{20}N_2O_2$ : N: 11.28%

Found: 11.14

4-Benzamido-4-hydroxymethyl-1-methylpiperidine from 4-Benzamido-4-carbomethoxy-1-methylpiperidine. This procedure is a modification of that given for the preparation of 1-benzamido-1-hydroxymethylcyclopentane (page 49). A mixture of 4.0 g. (0.014 m.) of 4-benzamido-4-carbomethoxy-1-methylpiperidine, 0.75 g. (0.014 m.) of potassium borohydride, and 0.9 g. (0.02 m.) of lithium chloride in 40 ml. of tetrahydrofuran was refluxed for 12 hrs. The mixture was cooled to room temperature, treated with 7 ml. of water and stirred for 6 hrs. Sufficient concentrated hydrochloric acid was then added in portions to make the mixture distinctly acid. The mixture was stirred for 4 hrs. at a temperature of 50°. Sufficient 20% sodium hydroxide solution was then added to make the mixture distinctly alkaline. The tetrahydrofuran layer was separated from the water layer which was then extracted once with tetrahydrofuran and twice with dichloromethane. The extracts and the original tetrahydrofuran layer were combined and evaporated to dryness in a current of air. The residue was washed successively with ether and water and then was air dried. It was recrystallized from tetrahydrofuran-acetone to afford 3.0 g. (86%) of product melting at 196-198° dec. The infrared spectra (identical) and mixture melting point (no depression) confirm the identity of this material with that obtained from the benzylation of the amino alcohol.

1'-Methyl-2-phenyl-2-oxazoline-4-spiro-4'-piperidine  
(8-Methyl-2-phenyl-3-oxa-1,8-diazaspiro(4.5)dec-1-ene).

The procedure for the preparation by Method I of 2-phenyl-2-oxazoline-4-spirocyclopentane (page 51) was followed. One half gram (0.002 m.) of 4-benzamido-4-hydroxymethyl-1-methylpiperidine in 3 ml. of benzene was treated with 8 ml. of thionyl chloride. After standing at room temperature for 24 hrs., the mixture was poured into 150 ml. of purified ether. The white solid which precipitated (presumed to be the oxazoline dihydrochloride) was immediately dissolved in 10 ml. of water. The resulting solution was made distinctly alkaline with 1 N sodium hydroxide and extracted 4 times with ether. The ether extracts were combined and evaporated to dryness in a stream of air. The residue was recrystallized from petroleum ether to give 300 mg (65%) of product melting at 85-86°. The infrared spectrum displays a sharp peak at 6.05 microns ( $1653 \text{ cm}^{-1}$ ) corresponding to the imine group (C=N) of the oxazoline ring.

Analysis:

Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$ :	C: 73.01%	H: 7.88%	N: 12.16%
Found:	72.51 M	8.26 M	11.78

No attempt was made to prepare the dihydrochloride of the oxazoline.

1'-Methyl-2-(p-methylphenyl)-2-oxazoline-4-spiro-4'-piperidine

4-(p-Methylbenzamido)-4-hydroxymethyl-1-methylpiperidine. The procedure given for the preparation of 4-benzamido-4-hydroxymethyl-1-methylpiperidine from 4-amino-4-hydroxymethyl-1-methylpiperidine was followed. Treatment of 3.0 g. (0.02 m.) of 4-amino-4-hydroxymethyl-1-methylpiperidine with 3.1 g. of p-methylbenzoyl chloride and 1.0 g. of sodium hydroxide in a water-chloroform medium afforded, after recrystallization from tetrahydrofuran-acetone, 1.8 g. (35%) of product melting at 183-184.5°. The infrared spectrum displays an NH absorption band at 2.98 microns (3356  $\text{cm}^{-1}$ ) and an amide carbonyl band at 6.10 microns (1640  $\text{cm}^{-1}$ ).

Analysis:

Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ :	C: 68.67%	H: 8.45%	N: 10.68%
Found:	68.90	7.97	10.44

1'-Methyl-2-(p-methylphenyl)-2-oxazoline-4-spiro-4'-piperidine (8-Methyl-2-(p-methylphenyl)-3-oxa-1,8-diazaspiro(4.5)dec-1-ene). The procedure for the preparation of 2-phenyl-2-oxazoline-4-spirocyclopentane by Method I (page 51) was followed. Treatment of 0.5 g. (0.002 m.) of 4-(p-methylbenzamido)-4-hydroxymethyl-1-methylpiperidine in 3 ml. of benzene with 8 ml. of thionyl chloride yielded, after addition of 150 ml. of purified ether, the

oxazoline dihydrochloride. The dihydrochloride was dissolved in 10 ml. of water, and the resulting solution was made distinctly alkaline with 1 N sodium hydroxide and extracted 4 times with ether. These extracts were combined and evaporated to dryness in a stream of air. The residue was washed with water and recrystallized from aqueous acetone to give 0.35 g. (76%) of the oxazoline melting at 112.5-114°. The infrared spectrum possesses the characteristic imine band at 6.04 microns ( $1656\text{ cm}^{-1}$ ).

Analysis:

Calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}$ :	C: 73.74%	H: 8.25%	N: 11.46%
Found:	73.47 M	7.97 M	11.34

## SUMMARY

1. Practical synthetic routes were established in the present work for the preparation of 4-spiro-2-aryl-2-oxazolines.
2. The following new compounds were synthesized as potential antitussive and/or medicinal agents:
  - a. 2-phenyl-2-oxazoline-4-spirocyclopentane
  - b. 2-(p-chlorophenyl)-2-oxazoline-4-spirocyclopentane
  - c. 2-(p-methylphenyl)-2-oxazoline-4-spirocyclopentane
  - d. 2-(p-nitrophenyl)-2-oxazoline-4-spirocyclopentane
  - e. 2-(p-ethoxyphenyl)-2-oxazoline-4-spirocyclopentane
  - f. 2-(p-dimethylaminophenyl)-2-oxazoline-4-spirocyclopentane
  - g. 1'-methyl-2-phenyl-2-oxazoline-4-spiro-4'-piperidine
  - h. 1'-methyl-2-(p-methylphenyl)-2-oxazoline-4-spiro-4'-piperidine
3. The following new compounds were prepared either as intermediates in the synthesis of the cyclopentane series of 2-oxazoline compounds or as a means of confirming struc-

ture assignments in this series:

a. 1-benzamido-, b. 1-(p-chlorobenzamido)-,  
c. 1-(p-methylbenzamido)-, d. 1-(p-nitrobenzamido)-,  
e. 1-(p-ethoxybenzamido)-, and f. 1-(p-dimethyl-  
aminobenzamido)-1-carbomethoxycyclopentane;

a. 1-benzamido-, b. 1-(p-chlorobenzamido)-,  
c. 1-(p-methylbenzamido)-, d. 1-(p-nitrobenzamido)-,  
e. 1-(p-ethoxybenzamido)-, and f. 1-(p-dimethyl-  
aminobenzamido)-1-hydroxymethylcyclopentane;

the hydrochlorides of 1-amino-1-cyclopentyl-  
methyl a. benzoate, b. p-chlorobenzoate, c. p-  
methylbenzoate, d. p-nitrobenzoate, e. p-ethoxy-  
benzoate, and f. p-dimethylaminobenzoate;

a. 1-benzamido-, b. 1-(p-chlorobenzamido)-,  
c. 1-(p-methylbenzamido)-, d. 1-(p-nitrobenzamido)-,  
and e. 1-(p-ethoxybenzamido)-1-chloromethylcyclo-  
pentane.

4. The following new compounds were prepared as  
intermediates in the synthesis of the 1-methyl-  
piperidine series of 2-oxazoline compounds:

- a. 4-amino-1-methylpiperidine-4-carboxylic acid
- b. 4-amino-4-carbomethoxy-1-methylpiperidine
- c. 4-amino-4-hydroxymethyl-1-methylpiperidine
- d. 4-benzamido-4-carbomethoxy-1-methylpiperidine

- e. 4-benzamido-4-hydroxymethyl-1-methylpiperidine
- f. 4-(p-methylbenzamido)-4-hydroxymethyl-1-methylpiperidine.

## REFERENCES

1. Cornforth, J. W., "Oxazole and Its Derivatives", in "Heterocyclic Compounds", (R. C. Elderfield, Editor), vol. 5, John Wiley and Sons, New York, N. Y., 1957, p. 377.
2. Nakanishi, K., "Infrared Absorption Spectroscopy-Practical", Holden-Day Inc., San Francisco, Cal., 1962, p. 38.
3. Wiley, R. H., and Bennett, L. L., "The Chemistry of the Oxazolines", Chem. Rev., 44, 465 (1949).
4. Gabriel, S., and Heymann, Th., "Über Darstellung und Eigenschaften einiger Oxazoline", Ber., 23, 2493 (1890).
5. Fry, E. M., "Oxazolines", J. Org. Chem., 14, 887 (1949); Fry, E. M., "Oxazoline Ring Opening", J. Org. Chem., 15, 802 (1950).
6. Wehrmeister, H. L., "Reactions of Aromatic Thiols with Oxazolines", J. Org. Chem., 28, 2587 (1963).
7. Crane, C. W., and Rydon, H. N., "The Alkaline Fission of Some 2-Substituted Dimethylethylsulphonium Iodides", J. Chem. Soc., 766 (1947).
8. Wehrmeister, H. L., "Condensations of Aromatic Aldehydes with Oxazolines and a New Synthesis of Cinnamic Acids", J. Org. Chem., 27, 4418 (1962).
9. Leffler, M. T., and Adams, R., "Aminophenyl-2-oxazolines as Local Anesthetics", J. Am. Chem. Soc., 59, 2252 (1937).
10. Billman, J. H., and Parker, E. E., "Amino Acids IV. Amino Acids Related to Serines", J. Am. Chem. Soc., 67, 1069 (1945).
11. Wehrmeister, H. L., "Periodate Oxidations of Oxazolines", J. Org. Chem., 26, 3821 (1961).
12. Boyd, R. N., and Hansen, R. H., "Sulfonic Acid Esters as Alkylating Agents: Formation of 2-Oxazolines", J. Am. Chem. Soc., 75, 5896 (1953).

13. Winstein, S., and Poschan, R., "The Role of Neighboring Groups in Replacement Reactions. XVII Complex Neighboring Groups. The Benzamido Group", J. Am. Chem. Soc., 72, 4669 (1950).
14. Johnson, W. S., and Schubert, E. N., "Ring Closure of the 2-Benzoylaminocyclohexanols. The Mechanism of Oxazoline Formation", J. Am. Chem. Soc., 72, 2187, (1950).
15. Gabriel, S., and Neumann, A., "Über eine Bildungsweise der Oxazoline", Ber., 25, 2383 (1892).
16. Bochemühl, M., and Knoll, R., "Basic Therapeutic Products From Imino Ethers of Higher Fatty Acids", U. S. patent 1,958,529 (May 15, 1934)(Chem. Abstr., 28, 4539 (1934)).
17. McCasland, G. E., and Horswell, E. C., "Heterocyclization of Epimeric Aminocyclohexanols. I. Oxazolines", J. Am. Chem. Soc., 73, 3744 (1951).
18. Lambert, R. F., and Kristofferson, C. E., "Reaction of Put ramidine with Epoxides. Preparation of 2-propyl-2-oxazolines", J. Org. Chem., 30, 3938 (1965).
19. Heine, H. W., and Proctor, Z., "Isomerization of N-p-ethoxybenzoylethylamine", J. Org. Chem., 23, 1554 (1958).
20. Heine, H. W., Fetter, M. E., and Nicholson, E. M., "The Isomerization of Some 1-Aroylaziridines II", J. Am. Chem. Soc., 81, 2202 (1959).
21. Engelmann, M., "Oxazoline Compounds (Local Anesthetics)", U. S. patent 2,027,031 (Jan. 7, 1936)(Chem. Abstr., 30, 1519 (1936)).
22. Guidicelli, R., Beauvallet, M., Chabrier, P., and Najer, H., "Sur L'action Vasculaire de Quelques Amino-2-oxazolines N-substituées", Compt. Rend., 247, 2494 (1958).
23. Gawron, O., and Keil, John, "Competitive Inhibition of Acetylcholinesterase by Several Thiazolines and Oxazolines", Arch. Biochem. Biophys., 89, 293 (1960).
24. Belleau, B., and Triggie, D. J., "Studies on the Chemical Basis for Cholinomimetic and Cholinolytic Activity Part I. The Synthesis and Configuration of Quaternary Salts in the 1,3-Dioxolone and Oxazoline Series", Can. J. Chem., 40, 1201 (1962).

25. Rebstock, M. C., "Antibiotics", in "Medicinal Chemistry", (A. Burger, Editor), Interscience Publishers Inc., New York, N. Y., 1960, p. 914.
26. Anigstein, L., and Whitney, D.M., "Antirickettsial Activity of a Synthetic Compound Related to Chloramphenicol", Texas Repts. Biol. Med., 10, 768 (1952).
27. Suzuki, M., Suzuki, Y., and Maruyama, M., "Antibacterial Activity of Chloramphenicol Analogs", Ann. Repts. Takamine Lab., 5, 88 (1953).
28. De Bonneville, P. L., and Luskin, L.S., "Oxazine and Oxazoline Derivatives Useful as Fungicides", U. S. patent 2,831,858 (April 22, 1958) (Chem. Abstr., 52, 16379 g (1958)); De Bonneville, P. L., and Luskin, L. S., "4,4-Dialkyl-2-vinyl- and 4,4-dialkyl-2-isopropenyl-oxazolines and 5,6-dihydro-4H-1,3-oxazines and their Spirans", Ger. patent 1,067,437 (Oct. 22, 1959) (Chem. Abstr., 55, 19960 a (1961)).
29. Stanley, M. M., and Astwood, E. B., "Determination of the Relative Activities of Antithyroid Compounds in Man Using Radioactive Iodine", Endocrinology, 41, 66 (1947).
30. Poos, G. I., Carson, J. R., Rosenau, J. D., Roszkowski, A. P., Kelly, N. M., and McGowin, J., "2-Amino-5-aryl-2-oxazolines. Potent New Anorectic Agents", J. Med. Chem., 6, 266 (1963).
31. Yelnosky, J., and Katz, R., "Sympathomimetic Actions of cis-2-Amino-4-methyl-5-phenyl-2-oxazoline", J. Pharmacol. Exptl. Therap., 141, 180 (1963); Roszkowski, A. P., and Kelly, N. M., "A Rapid Method For Assessing Drug Inhibition of Feeding Behavior", J. Pharmacol. Exptl. Therap., 140, 367 (1963).
32. Guidicelli, R., Beauvallet, M., Chabrier, P., and Najer, H., "Sur L'action Vasculaire de Quelques Amino-2-oxazolines N-substituees", Compt. Rend., 247, 891 (1958).
33. Bloom, B. M., "A New Class of Potent Central Nervous System Depressants", J. Am. Chem. Soc., 79, 5072 (1957).
34. Krupinska, J., and Rombiosa, R., "Pharmacological Properties of Some Oxazoline Derivatives", Dissertations Pharm., 14, 131 (1962) (Polish) (Chem. Abstr., 58, 849 f (1964)).

35. Bloom, B. M., "Naphthylaminooxazolines", U. S. patent 2,811,529 (Oct. 29, 1957)(Chem. Abstr., 52, 6412 a (1958)); Bloom, B. M., "Oxazolines and Ureas", U. S. patent 2,870,159 - 2,870,161 (Jan. 20, 1959)(Chem. Abstr., 53, 16153 d (1959)).
36. Moffett, R. B., "Central Nervous System Depressants VI. Polymethoxyphenyl Esters and Amides", J. Med. Chem., 7, 319 (1964)
37. Rosnati, V., and Misiti, D., "Synthesis and Pharmacological Properties of 2-Aryl-4-methyl-4-(carbamoyloxymethyl)-2-oxazolines", Rend. 1st. super. sanità., 23, 620 (1960).
38. Chappel, C. I., and von Seeman, C., "Antitussive Drugs", in "Progress in Medicinal Chemistry", (G. P. Ellis and G. B. West, Editors), vol. 3, Butterworth and Co., London, England, 1963, p. 89.
39. Gold, C., Cornell Conference on Therapy, 5, 1 (1952)
40. Doran, N. J., "Barbituric Acid Hypnotics", in "Medicinal Chemistry" (F. F. Blicke and R. H. Cox, Editors), vol. IV, John Wiley and Sons, New York, N. Y., 1959, p. 129.
41. Oldfield, W., and Cashin, C. H., "The Chemistry and Pharmacology of a Series of Cycloalkanespiro-5'-hydantoins", J. Med. Chem., 8, 239 (1965).
42. Craçoe, E. J., Woltersdorf, O. W., Baer, J. E., and Sprague, J. M., "Synthesis and Diuretic Activity of 3,3-Spiro-substituted Hydrothiazides", J. Med. Chem., 5, 896 (1962).
43. Rice, L. M., Gesechickter, C. F., and Grogen, C. H., "Spirans III, Azaspirans and Intermediates", J. Med. Chem., 6, 388 (1963); Grogen, C. H., Gesechickter, C. F., Freed, M. E., and Rice, L. M., "Spirans VII. Neuroleptics Derived from Azaspirans", J. Med. Chem., 8, 62 (1965).
44. Somers, T.C., and Handly, G. J., "1-Aralkyl-4,4-dialkylpiperidines as Hypotensive Agents", J. Med. Chem., 7, 784 (1964).
45. Ueberwasser, H., "Substituted 2-Aminoalkylcycloalkanes", Ger. patent 1,059,901 (June 25, 1959)(Chem. Abstr., 56, 355 f (1962)).

46. Ellis, G. P., Golberg, C., King, J., and Sheard, P., "The Synthesis and Antitussive Properties of Some Cyclopentane Derivatives", J. Med. Chem., 6, 111 (1963).
47. Doyle, F. P., and Mehta, M. D., "Antitussives", in "Advances in Drug Research", (N. J. Harper and A. B. Simmonds, Editors), vol. 1, p. 107, Academic Press, New York, New York, 1964.
48. Deltour, G., Mercer, J., Charlier, R., Prost, M., Finon, F., and Etzensperger, P., "Influence Du Remplacement Du Radical Phényle Par le Radical Propargyle Sur Les Effects Toxicomanogènes De La Phénéthyl-1 Phényl-4 Propionoxy-4 Pipéridine", Arch. Int. Pharmacodyn., 142, 493 (1963).
49. Tarbell, D. S., and Leister, N. A., "The Stability of Mixed Carboxylic-Carbonic Anhydrides", J. Org. Chem., 23, 1149 (1958).
50. van Tamelen, E. E., "The Mechanism of N - O Acyl Migration", J. Am. Chem. Soc., 73, 5773 (1951).
51. Fodor, G., and Kiss J., "Acyl Migration O - N in the Diastereomeric 2-Aminocyclohexyl Benzoates", J. Am. Chem. Soc., 72, 3495 (1950).
52. Martin, R. B., Parcell, C., "Hydrolysis of 2-Methyl-2-oxazoline. An Intramolecular O - N Acetyl Transfer Reaction", J. Am. Chem. Soc., 83, 4835 (1961); Martin, R. B., Hedrick, R. T., and Parcell, A. P., "Thiazoline and Oxazoline Hydrolyses and Sulfur - Nitrogen and Oxygen - Nitrogen Acyl Transfer Reactions", J. Org. Chem., 29, 3197 (1964).
53. Hanze, H. R., and Spear, R. J., "Identification of Carbonyl Compounds Through Conversion into Hydantoins", J. Am. Chem. Soc., 64, 522 (1942).
54. Goodson, L. H., Honisberg, I. L., Lehman, J. J. and Burton, W. H., "Potential Growth Antagonists I. Hydantoins and Disubstituted Glycines", J. Org. Chem., 25, 1920 (1960).
55. Connors, T. A., and Ross, W. C. J., "Some Derivatives of 1-Aminocyclopentanecarboxylic Acid and Related Compounds", J. Chem. Soc., Part 2, 2119 (1960).
56. Steiger, R. E., "Benzoylation of Amino Acids", J. Org. Chem., 9, 396 (1944).
57. Loretto, N. H., and Brown, J. H., "Use of Acetone Dimethyl Acetal in Preparation of Methyl Esters", J. Org. Chem., 24, 261 (1959).

58. van Tamelen, E. E., "A New Reaction: The Rearrangement of the Hydrochloride of cis-2-Aminocyclopentyl p-Nitrobenzoate", J. Am. Chem. Soc., 74, 2074 (1952).
59. Ratouris, R., and Behar, R., "Synthesis of 4-Amino-3-isooxazolidinone", Bull. soc. chim. France, 1258 (1957).
60. Vaughan, J. R., and Osato, R. L., "The Preparation of Peptides Using Mixed Carbonic-Carboxylic Anhydrides", J. Am. Chem. Soc., 74, 676 (1952).
61. Rinderknecht, H., Rebane, T., and Ma, V., "Synthesis of Carnosine, Anserine, and Isoanserine", J. Org. Chem., 29, 1968 (1964).
62. Diehl, J. F., and Bowen, D. O., "Synthesis of Tripeptides of 1-Aminocyclopentane-1-Carboxylic Acid", J. Med. Chem. 8, 274 (1965).
63. Mailey, E. A., and Day, A. R., "Synthesis of Derivatives of Alkylated and Arylated Piperidones and Piperidinols", J. Org. Chem., 22, 1061 (1957).
64. Shriner, R. L., Fuson, R. C., and Curtin, D. Y., "The Systematic Identification of Organic Compounds", 4th Edition, John Wiley and Sons, Inc., New York, N. Y., 1962, p. 275.

ABSTRACT OF  
THE SYNTHESIS OF 4-SPIRO-2-ARYLOXAZOLINES OF POTENTIAL  
PHARMACOLOGICAL INTEREST

BY

Paul Waddell Collins, Department of Chemistry and Pharmaceutical Chemistry, Medical College of Virginia, June 1966

Numerous and diverse physiological actions are found among 2-oxazoline compounds. No reports of the synthesis or biological testing of 4-spiro-2-aryl-2-oxazolines were found in the literature. On the basis of the known pharmacological activities of certain aza- and diazaspirans, it was felt that 4-spiro-2-aryl-2-oxazolines should possess medicinal activity. In particular, it was reasoned that the combination in a bicyclic spiro structure of the 2-oxazoline ring with rings systems commonly found in synthetic antitussive compounds might result in active antitussive agents.

The aim of this research was the synthesis of a series of 2-aryl-2-oxazoline-4-spirocyclopentanes and a series of 1'-methyl-2-aryl-2-oxazoline-4-spiro-4'-piperidines. Six members were to be prepared in each series in which the aryl group represents respectively, a phenyl, a p-chloro, p-methyl, p-nitro, p-ethoxy, and p-dimethylaminophenyl radical.

With the exception of the p-dimethylamino derivative, acylation of 1-aminocyclopentane-1-carboxylic acid gave

the corresponding amido acids, the methyl esters of which were reduced with lithium borohydride to the corresponding amido-alcohols. Dicyclohexylcarbodiimide was employed to produce 1-(p-dimethylaminobenzamido)-1-carbomethoxycyclopentane from p-dimethylaminobenzoic acid and 1-amino-1-carbomethoxycyclopentane after unsuccessful attempts to prepare it by the mixed carbonic anhydride method. Each amido-alcohol, on treatment with hydrogen chloride in chloroform, rearranged by N to O acyl migration to the corresponding 1-amino-1-cyclopentylmethyl p-substituted benzoate hydrochloride. On treatment with base these compounds rearranged to the original amido-alcohols by O to N acyl migration. This sequence of reactions confirmed the structure of the amido-alcohols.

Treatment of each amido-alcohol with thionyl chloride afforded the corresponding 2-aryl-2-oxazoline-4-spirocyclopentanes in good yields. The structure of these compounds was confirmed in each case by the infrared spectra and elemental analyses of the oxazoline and/or its hydrochloride. Furthermore, the structure of 2-(p-ethoxyphenyl)-2-oxazoline-4-spirocyclopentane was confirmed by a proton magnetic resonance spectrum.

Each oxazoline compound ( except the p-dimethylamino-derivative) was converted to the corresponding 1-(p-substitutedbenzamido)-1-chloromethylcyclopentane by treatment with a saturated solution of hydrogen chloride in dioxane. Each chloroamide compound ( except the p-nitro derivative) was converted to the corresponding

oxazoline by treatment with alkali in order to provide further evidence for the oxazoline structure of the products isolated from the thionyl chloride reactions.

4-Amino-1-methylpiperidine-4-carboxylic acid was obtained by both acid and alkaline hydrolysis of the corresponding hydantoin. 4-Amino-4-hydroxymethyl-1-methylpiperidine, which was obtained by the reduction of 4-amino-4-carbomethoxy-1-methylpiperidine with lithium borohydride, was treated with benzoyl chloride and p-methylbenzoyl chloride to give respectively, 4-benzamido-4-hydroxymethyl-1-methylpiperidine and 4-(p-methylbenzamido)-4-hydroxymethyl-1-methylpiperidine. 4-Benzamido-4-hydroxymethyl-1-methylpiperidine was also obtained by the reduction with lithium borohydride of 4-benzamido-4-carbomethoxy-1-methylpiperidine which was prepared by benzylation of 4-amino-4-carbomethoxy-1-methylpiperidine. 1'-Methyl-2-phenyl- and 1'-methyl-2-(p-methylphenyl)-2-oxazoline-4-spiro-4'-piperidine were prepared by treatment of the corresponding amido-alcohols with thionyl chloride.